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AFRICAN REGIONAL WORKSHOP ON CAPACITY-BUILDING AND EXCHANGE OF EXPERIENCES ON RISK ASSESSMENT AND RISK MANAGEMENT OF LIVING MODIFIED ORGANISMS
Addis Ababa, 23-25 August 2007

REPORT OF THE CANADA-NORWAY EXPERT WORKSHOP ON RISK ASSESSMENT FOR EMERGING APPLICATIONS OF LIVING MODIFIED ORGANISMS 4 - 6 JUNE 2007, MONTREAL, CANADA

Note by the Executive Secretary

1. The Executive Secretary is pleased circulate herewith, for the information of participants in the African Regional Workshop on Capacity-building and Exchange of Experiences on Risk Assessment And Risk Management of Living Modified Organisms, the report of the Norway-Canada Expert Workshop on Risk Assessment for Future Applications of Modern Biotechnology, which was held in Montreal from 4 to 6 June 2007.

2. The workshop was organized to generate information to assist the discussion on the potential need for additional guidance on specific aspects of risk assessment and risk management of living modified organisms, such as guidance focused on particular types and particular intended uses of living modified organisms at the fourth meeting of the Conference of the Parties serving as the meeting of the Parties of the Protocol.

3. The report is being circulated as it was received from the Government of Canada.

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REPORT OF THE CANADA-NORWAY EXPERT WORKSHOP ON RISK ASSESSMENT FOR EMERGING APPLICATIONS OF LIVING MODIFIED ORGANISMS 4 - 6 JUNE 2007, MONTREAL, CANADA

The third meeting of the Conference of the Parties serving as the meeting of the Parties of the Cartagena Protocol on Biosafety considered the issue of additional guidance on risk assessment. Based on the Report of the ad hoc Technical Expert Meeting on risk assessment held in Rome 2005, the meeting decided that at this time the priority issue for the Meeting of Parties was provision of training and implementation of the risk assessment/risk management provision of the Protocol on a general basis. The decision did however identify that there are potential gaps in the guidance for risk assessment for emerging applications of modern biotechnology, namely in trees, fish, veterinary applications and specific plant varieties. The issue of additional guidance will be addressed at the fourth meeting of Parties in 2008.

Norway, supported by Canada, offered to host a workshop on risk assessment for emerging applications of modern biotechnology, with the objective of the provision of information to assist the discussion on risk assessment and risk management at the fourth meeting of the Conference of the Parties serving as the meeting of the Parties to the Protocol.

The workshop addressed available guidance on risk assessment for emerging applications of modern biotechnology, identification of gaps in information or science that could impact on appropriate risk assessments and appropriateness of current models for risk assessment applied to emerging applications. Although the Protocol addresses risk assessments for contained use and environmental release, the discussion was focussed on risk assessments for environmental release and for field trials as a priority.

The workshop adopted the following recommendations, which are also contained in Part C of the report:

- The general principles and methodologies for risk assessment contained in Annex III to the Cartagena Protocol also apply to transgenic fish, trees, viruses and pharmaplants.
- There is insufficient guidance on how to perform risk assessment for GM fish and viruses.
- There may be a need to develop specific methodologies and specific protocols for generating data necessary to conduct risk assessments for the future applications of modern biotechnology, especially for transgenic fish, trees and viruses.
- All risk assessments of living modified organisms should be conducted on a case-by-case basis as the impacts depend upon the trait inserted, the recipient organism and the environment into which it is released.
- There is a need for additional data on several elements necessary to conduct risk assessments for all four types of transgenic organisms (fish, trees, viruses and pharmaplants). Further research is recommended to fill the knowledge gaps, inter alia the specific gaps identified during the workshop.
- Field trials may be a useful tool to generate data on the impacts of living modified organisms, but may give raise to particular concerns. Alternative models for generating data, as well as containment and confinement measures should be considered when appropriate. Baseline information on the specific organism in question is very important for risk assessments.
- There is value in considering the differences between highly managed systems such as cultivated fruit trees and the more variable cases such as some forest systems and animal wildlife, and whether the recipient organisms are domesticated, semi-domesticated or non-domesticated species.
- Existing guidelines, methodologies, baseline information and risk assessments should be made readily available through the Biosafety Clearing House and other relevant international databases.

PROCEEDINGS

I. INTRODUCTION

1. The Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety considered, at its third meeting, the issue of the need for additional guidance on risk assessment. Based on the report of the Ad hoc Technical Expert Meeting on Risk Assessment under the Cartagena Protocol on Biosafety, held in Rome from 15 to 18 November 2005, the Conference of the Parties serving as the meeting of the Parties to the Protocol decided that there was no need for additional general guidance but that the provision of specific guidance on risk assessment might be of use. Consequently the Government of Norway, supported by the Government of Canada, hosted the present workshop on risk assessment for emerging applications of modern biotechnology.

2. The workshop addressed the available guidance on risk assessment and identified gaps in information and science that could have and impact on both appropriate risk assessments and the appropriateness of current models for risk assessment when applied to emerging applications of modern biotechnology. It was expected that the present report would be submitted to the fourth meeting of the Conference of the Parties serving as the meeting of the Parties to the Protocol, as an information document.

II. PROCEDURAL REPORT

3. The workshop met from 4 to 6 June 2007 at the Headquarters of the International Civil Aviation Organization in Montreal, Canada.

4. 62 experts were present, including experts from among the Parties to the Protocol, from other Governments, and from relevant organizations. A full list of the participants is contained in annex II to the present report.

5. The meeting was opened at 9:00 a.m. on Monday 4 June 2007 by Ms Beate Ekeberg of Norway. She welcomed the participants and thanked the government of Canada for co-hosting the workshop with Norway. She also thanked the Executive Secretary of the Convention on Biological Diversity as well as the members of the steering committee, the chairs of the working groups and those making presentations. She noted that the workshop coincided with World Environment Day, being hosted by Norway on 5 June 2007, and observed that the theme of the workshop and of the World Environment Day were to some extent related.

6. Ms. Ekeberg said that risk assessment was one of the core elements of the Protocol. It was needed to contribute to an adequate level of protection against adverse effects on biological diversity, taking also into account risks to human health, and was thus an important first step in achieving the objectives of the Protocol. She observed that risk assessment involved the identification of potential adverse effects, the assessment of the likelihood that such effects would occur, as well as the assessment of the consequences that might arise from those effects should they occur. The purpose of the workshop was to identify available guidance on risk assessment. As risk assessment required scientific knowledge, it was necessary to establish what was known and what was not known. Thus risk assessment also had to address uncertainties, and the possible gaps in existing knowledge, as well as the appropriateness of the current models of risk assessment. The objective of the Protocol could only be achieved when decisions on whether or not to allow production and use of living modified organisms (LMO) are based on scientific knowledge and the precautionary principle in cases of scientific uncertainty. The outcome of the workshop would provide a valuable input for discussion of risk assessment by the fourth meeting of Conference of the Parties serving as the meeting of the Parties to the Protocol.

7. Ms Pat Dolan, Executive Director of the Outreach and Biodiversity Priority Directorate of Environment Canada, also welcomed the participants on behalf of the Government of Canada. She said that the subject of the workshop was both timely and significant as governments were being asked why

dangerous and risky activities were being allowed. Governments had to make decisions on whether new technologies were acceptable and to achieve that end they also needed to have a realistic assessment of the risks posed by new technologies. They needed to be able to make decisions about the types of risk, and the levels of risk involved with science and new technologies, and expert advice was needed that explained both the science and facts, or the lack of facts. Ms. Dolan also noted that the science of risk assessment was evolving rapidly and she hoped that the workshop would provide additional guidance on that subject.

8. Mr. Charles Gbedemah, welcomed participants on behalf of the Executive Secretary of the Convention on Biological Diversity, Dr. Ahmed Djoghlaf, and extended warm thanks to the governments of Norway and Canada for organizing and funding the workshop. Mr. Gbedemah recalled the guidance provided by the Sixth Conference of the Parties to the Convention regarding the priority of providing training and capacity-building for biosafety-related risk assessment and risk management. He said that guidance was also required to deal with risk assessment for emerging applications of modern biotechnology. It was further necessary to identify gaps in information or science that could have an impact on proper risk assessment, and to examine the appropriateness of existing models for risk assessment in relation to contained use and environmental release. In closing, Mr. Gbedemah extended special thanks to the members of the Workshop's Steering Committee, and wished participants fruitful deliberations.

9. The meeting adopted its agenda on the basis of the provisional agenda proposed by the steering committee.

10. Ms Beate Ekeberg (Norway) and Mr. Desmond Mahon (Canada) served as co-chairs of the workshop.

11. Mr. Mahon gave participants a brief overview of the workshop's context, organization and objective. He stressed that the workshop was designed to gather the participants' specific scientific advice. No policy issues would be discussed, and no consensus on the issued would be required. Mr Mahon also said that the background documents on the four topics of the workshop that had been distributed to the participants before the meeting were only intended as introductions to the topics, and were not intended to be defintive or govern the discussions The desired output of the workshop was a document containing broad recommendations arising out of a fact-based scientific approach informed by the personal perspective of the experts in attendance. The recommendations would be compiled and presented as an information document to the fourth meeting of the Conference of the Parties serving as the meeting of the Parties to the Protocol as input for the negotiations and discussions on risk assessment.

12. At its first plenary session, the workshop established four working groups: Working Group I, with Dr. Marja Ruohonen-Lehto (Finland) as chair, considered the issue of transgenic fish; Working Group II, with Dr. Bao-Rong Lu (China) as chair, considered the issue of transgenic trees; Working Group III, with Dr. M. Burachik (Argentina) as chair, considered the issue of pharmaplants; and Working Group IV, with Dr. H. Gaugitsch (Austria) as chair, considered the issue of genetically modified viruses for the management of animal populations.

13. At its first plenary session the workshop also heard presentations on subjects of transgenic fish, by Dr. R. Devlin, and transgenic trees, by Prof. K.M.A. Gartland.

14. At its second plenary session on 5 June 2007 the workshop heard presentations on the subject of pharmaplants, by Dr. A. Alvarez-Morales, and on genetically modified viruses for the management of animal populations, by Dr. T. Traavik.

15. Discussions that took place in the working groups are reflected in section III A of the present report.

16. At its third plenary session on 6 June 2007 the workshop considered the reports by the chairs of the working groups on the discussions that had taken place on the subjects of transgenic fish and

transgenic trees. The reports of the chairs, as orally amended by the participants, are contained in section III B to the present report as the conclusions of the workshop on those subjects.

17. During the adoption of the report of the working group on genetically modified trees, one participant who had not been present during the discussions of that working group made a comment. In order to avoid reopening the debate, it was proposed by the Co-chair that the comment be included in the report of the meeting.

18. The comment related to the issue of field trials of genetically modified trees. The participant expressed his understanding that very high risks were involved, and stated that some experts recognized that it was important to identify high risk cases of genetically modified trees that should not be studied using flowering trees in open field trials

19. At its fourth plenary session on 6 June 2007 the workshop considered the reports of the chairs of the working groups on the discussions that had taken place on the subjects of pharmaplants and the use of genetically modified viruses for the management of animal populations. The reports of the chairs, as orally amended by the participants, are contained in section III B to the present report as the conclusions of the workshop on those subjects.

20. During the adoption of the report of the working group on pharmaplants, it was decided that some of the proposed amendments that were not incorporated into the final working group report could be included in the text of the procedural report for the meeting as a whole.

21. One such comment related to the fact that guidance for risk assessment could become unclear with regard to effects on human health. Particularly with regard to risk assessment of pharmaplants, it was important to remember that humans should be seen as part of the environment, and that, for instance, health effects should be seen in the context of farm workers exposed to pharmaplants.

22. With regard to the elements to be included in risk assessments, one participant stated that, in his opinion, it was always appropriate to include gene stability, and that gene stability should furthermore be followed up during monitoring and risk management.

23. In relation to the issue of the risks associated with expression of the pharmaceutical compound in pharmaplants, one participant pointed out that the efficiency of tissue specificity for expression of a compound could be highly important to consider in relation to potential feeding of animals on some parts of the concerned plant.

24. In the section on issues to take into consideration for risk management, one participant wished to include a statement to the effect that risk management methods were typically very important for trials involving pharmaplants.

25. In the same section, some indicated that ease of or efficacy of confinement measures may increase as scale decreases.

26. At its fourth session the co-chairs also presented a chair's text for consideration by the participants as the recommendations of the workshop. The recommendations of the workshop, as orally amended by the participants, are reflected in section III C to the present report.

27. The workshop held four plenary sessions and each working group held two sessions.

28. After the customary exchange of courtesies, the workshop was closed at 6:00 p.m. on Wednesday, 6 June 2007.

III. SUBSTANTIVE REPORT

A. Consideration of issues of risk assessment

Transgenic Fish

29. Dr. R. Devlin introduced the subject of living modified fish , hereafter referred to as transgenic fish, during the first plenary session of the workshop on 4 June 2007. The issues addressed included the scope of genetically engineered aquatic organisms, transgenic fish models for environmental risk assessment research, the information needs and experimental approaches for risk assessment, modelling, the major issues affecting reliability of laboratory-driven risk assessment data, containment strategies and their efficacy, and the perceptions of the media, industry and the public. He reminded the participants that sixty-eight per cent of all fish extinctions in the previous century in North America had resulted from the introduction of foreign species. The introduction of fish with novel characteristics into ecosystems was therefore of concern because major ecological disruptions could occur that would be difficult to predict. Among the issues to be considered were: the risk of escape from physical containment, the direct effects of escaped fish on the ecosystem, and the sustained effects of interbreeding and persistence of transgenic fish.

30. Dr. Devlin explained that risk assessment data could differ depending upon the traits being modified. Currently genes were being transferred to transgenic fish to modify: metabolism, growth, reporters, development, physiology, susceptibility to disease and reproduction. He also noted that it was neither currently allowed, nor was it desirable, to release fertile genetically modified fish into the natural environment for assessment of the ecological consequences of survival and reproductive fitness. Instead individual characteristics would need to be examined under controlled laboratory conditions, or in semi-natural environments. Non-transgenic animal surrogates could also be used.

31. The limitations of predictions made from laboratory studies resulted from the inability to determine the magnitude of real-world effects. Opposing fitness effects arising from the genetic modification, as well as undetected pleiotropic effects meant that there were large assumptions associated with converting laboratory observations into evaluations of true fitness consequences. He stressed that nature was vastly more complex than the laboratory and noted that background genetics might also influence the expression of a transgene. While laboratory risk assessment data could identify the forces at work, it could not identify their true magnitudes in nature.

32. Working Group I took up the issue of transgenic fish and at its first session the chair, Dr. Marja Ruohonen-Lehto, reminded the participants that the purpose of the workshop was to provide scientific guidance and suggested that the participants use the neutral term impact or effects rather than harm or hazard in their deliberations.

33. In the discussion that followed it was noted that there were varying perceptions of the benefits of transgenic fish. One area of concern was the dispersal and invasion of transgenic fish into new habitats. However it was pointed out that it was unclear to some participants whether the dispersal of the fish or the gene was at issue. It was asked whether the emphasis was being placed on the pathway or the outcome.

34. What made fish different was that they were not domesticated and that they move freely. Issues of the containment, management and control of the migration of fish were therefore of importance. Gene flow to related species, and effect of transgenic fish on whole ecosystems, also raised concerns and it was suggested that data on the food web, disease, competition, and predators were required. It was also felt that the differences in the effects of aquaculture, the release into the environment and land-based aquaculture needed to be considered further, as did issues of detection and biomarkers.

35. The specific impact and effect of transgenic fish needed to be compared with non-transgenic fish in the context of each species, but it was noted that while there was information on salmon, there was less information on other species of fish. While basic ecological studies were needed for all fish, it was suggested that salmon could be used as a case study to get insight into the broader questions to be asked. Others felt that there was a need for case studies beyond the study of salmon, and that other geographic areas had to be considered as well.

36. A need for reliable models for ecosystems was also indicated. In the case of salmon, because of unknown variables, none of the models used in the previous century had predictive value. Models had to

be based on detailed knowledge of the environment they represented and are only as useful as the information on which they were based. It was suggested that there was a need for systematic studies of the environments in question. It was also pointed out that models were developed that addressed different levels of organization, including physiological, ecological, and genetic and for the evaluation of the ecosystem.

37. Some participants expressed concern that the impact of transgenic fish on human health was being overlooked and stressed that it was important to consider how people responded to transgenic fish as well as the use of transgenic fish as food. It was also noted that article 26 of the Protocol dealt with the socio-economic considerations arising out of the use of living modified organisms and it was suggested that it was important to consider those issues as well.

38. Some participants also expressed concern at the lack of clarity in the terms being used and said that when engaging in risk assessment it was important to know what questions were really being asked. They also wondered whether the working group was replicating the work of the *Codex Alimentarius* Commission on transgenic food or of the Organisation for Economic Co-operation and Development (OECD) on transgenic salmon. Others however noted that the work of the *Codex Alimentarius* Commission excluded the environmental impacts of transgenic food and that the work of the OECD on transgenic salmon was a compilation of data and did not deal with risk assessment *per se*. The participants were informed that the OECD working group had only started its work on risk assessment considerations, and that the results of that work would be presented separately.

39. Following the discussion the chair said that she would prepare a text on conclusions reflecting the issues that had been raised during the discussion for presentation to the third plenary session of the workshop. She asked those who wished to participate in the drafting of the text to meet with her informally.

Transgenic Trees

40. Prof. K.M.A. Gartland introduced the subject of living modified trees, hereafter referred to as transgenic trees, during the first plenary session of the workshop on 4 Junes 2007. He began his presentation by pointing out that, for the purposes of risk assessment, trees could be seen as bigger, longer-lived plants that reached reproductive maturity later in life. Long experience with genetically modified agricultural crops could therefore provide lessons for considering risk assessment of genetically modified trees. He pointed to the various applications of genetically modified trees, highlighting the relative benefits of genetic modification in controlling pathogens, disease and pests, as well as in increasing food, fuel and fiber production. Environmental benefits also arose from the ability to genetically modify trees' processing properties to extract products more effectively and with less waste.

41. Prof. Gartland went on to describe trials involving various genetically modified trees. Although the technology had proven effective in a laboratory setting, social concerns with regard to trans-gene stability, gene flow, fitness effects, pathogen resistance, soil ecosystem effects, human and environmental health effects, and ecosystem disruption of non-target organisms sometimes prevented deployment of genetically modified trees in the environment. Given the potential benefits of genetically modified trees, and the need to know more about the actual risks associated with their deployment, it was of the utmost importance to set up systems for modeling and small-scale, controlled release of such trees. Appropriate containment and biological confinement methods were required to make it possible to allow transgenic trees to flower. Long-term monitoring was essential to measure the effectiveness of genetic modifications in achieving their intended purpose, and to assess the risks involved.

42. On the specific topic of systems modeling, it was necessary to include components of genetically modified tree-ecosystem interactions. There was also a need to create a meta-model to build on the fragmentary conclusions of small-scale models. This could be followed by small-scale, limited release of

genetically modified trees, perhaps with genetic traits designed to prevent fitness effects, to report on gene expression, and to track gene behaviour. That would help validate models and provide better results on which to base risk assessment.

43. Prof. Gartland concluded by saying that the Convention on Biological Diversity and the Biosafety Protocol provided excellent risk assessment tools for the agricultural sector that could be used as an effective framework for risk assessment of genetically modified trees. Such a framework had to be based on rational science, and concentrate on key questions and lessons learned from agricultural crops and from contained models. That way, there could be case-by-case review informed by previous practice.

44. Working Group II took up the issue of transgenic trees. The Chair of the working group on transgenic trees, Dr. Bao-Rong Lu began the session by calling on participants to focus the discussion on what made trees different from plant crops with regard to risk assessment. Participants then heard a presentation by Dr. Meng-Zhu Lu on risk assessment for commercial transgenic poplar plantations in China.

45. During his presentation, Dr. Lu provided a timeline for releasing transgenic trees into the environment in China, and outlined the various steps involved in the corresponding laboratory and field trials. The trials had examined factors such as toxicity, gene stability, soil microorganisms, insect populations and gene flow. No significant risks with regard to any of those issues had been found in the transgenic poplar plantations. However, changing variables made findings differ enough to conclude that risk assessments of transgenic trees had to be conducted on a case-by-case basis. One example of this was gene flow, which was affected by wind, temperature, rain, trees surrounding the sites, and other factors, such as competition between transgenic and non-transgenic trees. Further funding and longer-term studies in particular were required to achieve a greater understanding of how potential risks would be affected by trees' longevity.

46. Following the presentation, a discussion took place in which a number of general issues were raised. The chair of the working group asked the participants for their views. One major issue was whether the framework for performing risk assessments as contained in Annex III to the Cartagena Protocol on Biosafety, could be applied to transgenic trees, or whether a whole new paradigm was required. Several participants expressed the view that Annex III provided valid parameters. Their relevance to transgenic trees depended on the extent to which each category of tree give rise to considerations similar to those that are to be taken into account according to the Cartagena Protocol.

47. It was pointed out that trees, unlike most crops, were perennial. The longevity of trees raised particular issues with regard to monitoring and the long-term effects of genetic modification. Another special characteristic was the existence of both human-managed tree plantations and wild tree stands, which led to different consideration of each type of tree. Finally, the fact that flowering trees were difficult to contain meant that particular attention had to be paid to the risk of potential spread of a gene that could render a particular species dominant in the natural environment.

48. It was therefore very important to understand the risk of a spread of transgenic trees owing to a large fitness benefit. Fitness was affected by many variables, such as the genetically modified trait, the genetic background of the host organism, the size and structure of the tree population, the geographical environment, and even climate change. The impacts of such a spread into the natural environment included destruction of biological diversity, and of non-target organisms living within the trees' ecosystem. The magnitude of the destruction would be even greater if the spread reached a centre of origin or centre of diversity of the host tree.

49. Risk assessment for transgenic trees would entail filling the knowledge gaps associated with the above factors. That meant gathering baseline data on the risks linked to genetic changes for different purposes. It also meant learning more about trees' life cycles, about the micro-organisms and food webs associated with trees, and about their managed or natural environments. Furthermore, when it came to comparing genetically modified trees and genetically pure trees for risk assessment purposes, a number of additional factors had to be taken into account, such as any other modifications to which pure trees might be subject, including pesticides and traditional breeding practices.

50. Non-tree-related considerations for risk assessments included human health impacts and the need to investigate the relationship between gene modifications and the allergenic properties of pollen. It was also mentioned that the proposed reasons for the genetic modification would have an effect on the perceived social acceptability of a given risk.

51. Finally, the desirability of conducting field trials to gather all of the relevant information was discussed. Protocols would be needed to circumscribe such trials, both to ensure maximum confinement and to extract the maximum amount of information for risk assessment purposes. A step-wise approach similar to that used for transgenic plant crops could be adapted to the special characteristics of trees. It would be necessary to proceed on a case-by-case basis, with case categories gradually getting bigger as the body of knowledge grew. It was also important to try to prevent field trials and deployment from tipping over from risk assessment into risk management, and to keep in mind that long-term monitoring required substantial resources, which developing countries often lacked.

52. Following the discussion, the Chair of the working group undertook to prepare draft conclusions taking into account the issues raised. The reference documents mentioned by participants during the discussions would be included in a bibliography to be forwarded as an annex to the report of the workshop meeting.

Pharmaplants

53. Dr. Alvarez-Morales introduced the subject of pharmaplants, living modified plants genetically modified to produce pharmacologically active compounds, at the second plenary session of the workshop on 5 June 2007. During his presentation, Dr. Alvarez-Morales said that several projects for genetically modified pharmacologically active plants were being considered for commercialization by various biotechnology firms, other organizations, industry and public research groups. Countries that might have the capacity to develop their own genetically modified plants faced other constraints as well. Clear, strict guidelines for risk assessment were necessary, as research into genetically modified plants for pharmacological purposes could be used to solve pressing social problems.

54. Dr. A. Alvarez-Morales proposed that field trials could follow the protocols used so far for experimental release, which exercise very strict control to prevent transgene escape through pollen flow or seed dispersal. There were, however, knowledge gaps with regard to the effects of new substances on non-target organisms and animals, and their cumulative effects throughout the food chain. That begged the question of whether field trials were in fact desirable. Contained crop production made it possible to control risks far more effectively. It was also possibly more cost-efficient than research into acute and-or chronic exposure of non-target organisms and food-webs to genetically modified material.

55. He went on to describe the risk-assessment procedure applied to a project in Mexico to perform a field trial of bananas that had been genetically modified to produce antigens derived from rotavirus. The project had been conducted by a research institute, which had based its choice of crop on a number of factors designed to minimize risk. Those factors were the absence of wild relatives of the host plant, the presence of vegetative propagation, the fact that a single plant produced enough material for testing, the feasibility of completely isolating the plant, the ease with which fruits could be accounted for and controlled, and the ease of post-harvest control.

56. In addition to incorporating such factors, moving ahead in the area of risk assessment meant developing a definition of which plants could be genetically modified. It was also necessary to find efficient ways to ensure isolated environments that excluded non-target organisms and animals, while allowing for the production of sufficient amounts of genetically modified pharmaceutical material. Risk management strategies and contingency plans were of the utmost importance, as were strict monitoring methods and surveillance mechanisms, as well as mechanisms to trigger preventive or corrective measures in a timely manner in the event of transgene escape. National policies on these issues, reflecting a case-by-case approach based on the particular problems of each country, could be a component of risk management, as long as the regulatory burden did not prevent forward movement in this area.

57. Working Group III also took up the issue of pharmaplants. The chair of the working group, Dr. M. Burachik, asked the working group to begin with a brainstorming session aimed at pinpointing issues specific to the risk assessment of genetically modified plants for the production of pharmacological substances (pharmaplants), to be used as a springboard for discussion. The issue of scope gave rise to some debate about what such a risk assessment should cover. While many of the risk factors of pharmaplants were no doubt relevant to other biomedical and industrial applications on a case-by-case basis, the scope of risk assessments in this case would be limited to plants in which genes had been inserted for the expression of active pharmaceutical compounds for therapeutic, diagnostic and vaccination purposes.

58. There was also some discussion regarding the fact that the nature of pharmaplants and their attendant risks blurred the limit between risk assessment and risk management. That was because, contrary to genetically modified agricultural crops, the worst-case scenario for pharmaplant crops was to have the bioactive compound enter the food stream. There was also a greater potential impact if pharmaplants were accidentally released into the environment with a gene giving them a selective advantage. That meant that the focus of risk assessment was containment, not release. The nature of the genetic modifications, the types of pharmaplant crops, and the intended use of the pharmaplants all provided additional elements to be considered when conducting risk assessments.

59. The bioactive compound inserted into the pharmaplant affected risk in a number of ways. There was, of course, the compound's toxicity and allergenicity. The level of expression of the compound also had a direct effect on risk, since the more biologically active it was, the greater the effects it was likely to be in the event of release. It was furthermore important to ascertain tissue specificity of the expression of the compound, but to look at the entire plant when assessing risks for non-target effects. The presence of multiple new genes or genetic modifications could create phenotypic effects other than the desired protein expression. The persistence of bioactive compounds, or their stability in the environment was also a key consideration, as long-lasting bioactive material could have chronic effects. Compounds to be used for vaccination created the potential of affecting human immunity, as exposure over time to a sub-unit of a vaccine could increase tolerance and render the vaccine ineffective. Finally, some bioactive compounds could reproduce, replicate and recombine, increasing their associated risks. It was therefore important to measure these elements when conducting risk assessments.

60. The nature of the crop used to host the bioactive pharmaceutical compound had a bearing on both the effectiveness of the genetic modification and its attendant risk. It was therefore useful to know which crops could be used and which should be avoided. Although pharmaplant crops tended to be smaller in scale than other genetically modified crops, even very small releases could contaminate the food chain. One approach to prevent food contamination was to use minor or non-agricultural crops as a platform for the genetic modification. While that tended to solve one problem, it created another in the form of lack of familiarity with the basic biology and other characteristics of the host crop. That raised the related issue of what could be used as a baseline to compare risk. Neither conventional nor genetically modified agricultural crops qualified in this respect. Information on all of the above factors was therefore needed for risk assessment.

61. The intended use of the pharmaplant raised a number of concerns. One such concern was precisely the fact that, although the host plants might be edible, in many cases the inserted pharmaceutical compound made them completely inedible. Conversely, the possibility of having pharmaplants that could be eaten as a means of administering the pharmaceutical compound they contained, e.g. oral vaccines, raised a series of questions regarding the ability to measure the variability of bioactive material concentration. It also posed difficulties with regard to safeguards against unintended consumption of the bioactive material and possible routes of distribution and accidental release. If the pharmaplant was intended to be processed to extract the pharmaceutical compound, it was necessary to learn about the bioactive compound's potential for escaping the production stream, as it is accomplished through good manufacturing practices.

62. Following the discussion, the Chair of the working group undertook to prepare draft conclusions taking into account all of the issues raised.

Genetically modified viruses in the management of animal populations

63. Dr. T. Traavik introduced the subject of genetically modified viruses for the management of animal populations at the second plenary session of the workshop on 5 June 2007. In his presentation Dr. Traavik said it was difficult to extrapolate from cells, and that even virus families were so different that it did not make sense to extrapolate from one virus to another. He recalled that a Noble Prize winner, A. Lwoff stated that viruses were viruses, thereby indicating their unique character.

64. Genetic modifications could be achieved by homologous recombination to achieve gene deletion and by transgenesis, or by both. Some of the viruses being modified were: *Poxviridae* including orthopox and avipox; *Adenoviridae*, most commonly human Adenovirus type HAd5, *Herpesviridae* and *Togaviridae*, as well as other host species specific viruses. Environmental implications were found in applications of gentically modified viruses relating to livestock vaccines, wild life reservoir species vaccination, pest animal population control, and human vaccines. Genetically modified viruses maybe recombinant replicating or non-replicating virus-vector vaccines. The benefit of recombinant, non-replicating virus-vector vaccines was that they provided good protective immune responses, including at the mucosal portal-of-entry. They were also simple and cheap to produce, could provide a rapid response to emerging diseases, were resistant to degradation, could be made non-persistence and and did not perform or carry out genomic and foreign integration. Some of them make it posssible to produce multivalent vaccines.

65. However there were risks and drawbacks to genetically modified viruses as they could create non-target infections. It was also unclear whether such recombinant, non-replicating virus-vectors were really replication deficient. If a virus did not replicate in one cell line that did not mean that it would not replicate in another. Risks were also posed by the possibilty of a double infection with a naturally occuring virus and a vaccine virus resulting in a new hybrid. The efficiency of genetically modified vaccine vectors may be diminished by preexisting anti-vector immunity.

66. Dr. Traavik also gave the example of Modified Vaccinia Ankara (MVA) being crossed with cowpox and said that after several passages it had no longer been possible to detect the transgene. He

also noted a naturally occuring case of a recombinant ectromelia and cowpox that had been isolated in a patient in Norway, although ectromelia was not naturally occuring in Norway. International regulatory groups had also recently questioned the safety of certain existing vaccine constructs and their production systems. Dr. Traavik said that while the main focus of research has previously been on the functionality and immunological mechanisms of viruses, work on safety aspects most often was put off until later in the development process . By then making fundamental changes to the vaccine to improve its safety could be costly and time-consuming. He noted that the public might also lose confidence in such a process.

67. In closing Dr. Traavik highlighted a number of gaps in the current knowledge of viruses which related to naturally occurring relatives and new viruses created through recombination, non-target effects, the transboundary and trans-ecosystem spread and vectors of transport such as migrating birds, animals, insects, and ticks. There was also a lack of knowledge concerning the integration of GMV DNA, or fragments of it, into host cell chromosomes; as well as concerns about the genetic stability and deletion of transgenes and the influence of such ecosystem changes as temperature rise and chemical pollutants.

68. Working Group IV took up the subject of genetically modified viruses for the management of animal populations. The chair of the working group, Dr. H. Gaugitsch, asked the participants to take stock of the current state of the art as well as the guidance available for risk assessment, the available risk assessments and the current research on risk assessment.

69. In the discussion that followed, it was asked whether the stability of modified viruses could be assumed. It was also pointed out that during the vaccination campaigns against smallpox other species had been affected as well. Buffalo pox might have come from that process and there was evidence to show that a new cattlepox virus in Brazil might have developed out of that vaccination process as well. There was therefore a need to consider the spread to non-target species where there could be new expression of genes.

70. It was suggested that for the purposes of risk assessment, viruses could be grouped into diseases in humans and livestock populations and viruses for the control of wild species. In the first case, non-replicating viruses were desirable while in the control of wild species replicating viruses were needed. The issue of the effectiveness of genetically modified viruses was also raised, as was the issue host specificity and the ecological effects of viruses. It was suggested that it was important to consider disease ecology and the interaction between humans, animals and other organisms. While data was available from the science of virology, there was a lack of information in field situations.

71. Although viruses had often been seen as a special case for the risk assessment, it was suggested that the model of biological control agents could set the pattern for the risk assessment of genetically modified viruses. Others noted that the issue of risk assessment was not unique to genetically modified viruses and that phytosanitary and veterinary regulations were already in place. International standard setting organizations were also working on the issue, as was a task force of the *Codex Alimentarius*. An ad hoc group on biotechnology of the World Organization for Animal Health (OIE) was also considering the issue, and it was suggested that the work of the International Embryo Transfer Society was also a possible source of guidance on safety issues. The European Medicines Agency (EMEA) also had in place guidance on live recombinant vector vaccines for veterinary use.

72. One participant noted the use of the vaccinia virus when targeting rinderpest and stressed that in east Africa, human and livestock lived in close proximity. That needed to be taken into consideration, as did the difficulty of transferring use of small animal model to larger hosts such as cattle. It was also reported that in Australia it had been difficult to move from the laboratory when developing viruses to control rabbits, mice and foxes. Viruses had however been used to vaccinate foxes against rabies in northwest Europe and raccoons in the United States of America, although it was unclear how successful that had been.

73. Little research had been done that gave a holistic approach to the environmental effects of viruses, and it was felt that further work in the area was needed. The participants also felt that the issue of ecological and environmental effects had not been given sufficient consideration, and insufficient consideration had also been given to the spread of viruses across biological borders. Instead the issue had generally been considered from a medical or veterinary point of view. Epidemiological studies had only studied the incidence of the expression of a disease and not the existence of the virus in asymptomatic populations. New viral species might not be detected or else they might not show in the form of detectable symptoms.

74. However it was also noted that new technologies such as PCR allowed for greater refinement in research into virus types. But better research tools were also needed, and research capacity had to be developed. It was also suggested that the use of stem cells might be a way forward. One participant also informed the working group of ongoing work on the effect of myxoma virus in rabbits on their avian and animal predators.

75. The Chair thanked the participants for their contributions to the stock taking exercise and asked them for their views on the gaps in information necessary to perform risk assessments and the issues of note in the risk assessment of genetically modified viruses.

76. The participants were of the view that there was a lack of information on the biology of the host viruses and that there was also a need for research into the development of viral expression in hosts. Adequate follow-up of non-clinical carriers of viruses was also needed and it was necessary to study the effect of regional and seasonal patterns on viruses as well as the co-evolution of the viruses with their hosts.

77. It was also felt that much of the current research on viruses in cell lines was not predictive of viral behaviour in nature and that the portals of entry for viruses was often not adequately investigated. It was suggested that it would be better to use whole animals for such research. Generally there were serious knowledge gaps, especially related to whether a particular species was permissive or non-permissive, and it was pointed out that such distinctions often varied within the same animal depending on age, sex, hormones, seasons and other environmental factors.

78. It was also suggested that there was not enough baseline data to make such assessments. Targeted experiments were needed to gain better knowledge of virus ecology and virus/host interactions There was also a need to study the issues of ethnographic management systems and the socio-economic effects on populations. There was a need to encourage North-South collaboration in research and it was also suggested that there was a need for further consideration of the issues of metagenomics and bioinformatics.

79. Following the discussion the chair said that he would prepare a text on conclusions reflecting the issues that had been raised during the discussion for presentation to the third plenary session of the workshop.

B. Conclusions of the workshop

Transgenic Fish Session

Chair: Marja Ruohonen-Lehto (Finland)

1. Summary of Session

Discussions on environmental risk assessment of transgenic fish were opened with an overview of major areas of concern specific to this topic. Subjects such as control and containment of GM fish populations through to interactions of released GM fish with complex aquatic ecosystems were explored. Major gaps in the knowledge centered on the dearth of information available on the biology and ecology of many fish

species, creating difficulties in analyzing differences one might observe in transgenic fish with this lack of comparators. Discussion of methodologies which may aid in bridging these gaps included consideration of models and comparators, as well as near-nature laboratory experimentation.

2. Considerations for Environmental Risk Assessment of Transgenic Fish

The general principles and methodologies as described in Annex III of the Cartagena Protocol also cover transgenic fish. The framework for risk assessment offered by the Protocol can therefore be used to address specific issues raised by transgenic fish.

Issues unique to fish

Some issues related to environmental risk assessment were identified as specific to fish. Fish species used thus far for genetic modification are undomesticated, wild animals that move easily to different, possibly large geographical areas and display indeterminate growth. Moreover, fish has the potential for rapid population expansion and are ectothermic by nature and thus quite sensitive to changes in abiotic conditions. Introduction of fish into new environments is highly uncontrolled and fish will interact with many different species in broad areas through dispersal. It was noted that no field trials can be carried out with transgenic fish and this highlights the importance of careful laboratory experimentation using near-nature conditions and surrogate models.

Consideration of the GM fish in its environment

The following elements were considered to be important in assessment of transgenic fish: species or strain of fish; gene construct, insertion site and trait stability; pleiotropic effects of the inserted genes; life history traits of the fish including high fecundity, induced sterility, specific ecosystem in which the fish is found; environmental context e.g. diversity, variability, availability of suitable comparators (wild type or other strains with similar phenotypes). Data from comparators are useful for formulating hypotheses and specific questions for risk assessment and are important for conducting case-by-case risk assessments.

Whole ecosystem effects

Whole ecosystem effects include those occurring directly from introduced animals as well as effects arising from persistence of these animals in the environment through reproduction in nature. Consequences arise from phenotypic characteristics of the transgenic fish, in addition to their number (population) in the ecosystem (introduction rate and fitness including ability to reproduce). The ecological niche which the fish inhabits in the complex aquatic food web may be affected by introduction of a transgenic fish. Interactions with the environment and other organisms, disease susceptibility, competition, and effects on predators, prey and related species all form part of the total effect the transgenic fish will have on the ecosystem. Further, abiotic factors such as climate change and pollution may affect the behaviour or fitness of the transgenic fish in the ecosystem, producing downstream effects on all the factors mentioned above including possible effects on biodiversity.

In addition it was noted that information on environmental effects of transgenic fish can benefit from the experience that we have on introduction of non-indigenous fish species into the environment. Moreover, research has shown that it is important to study a certain genotype in several ecological milieus. Effects are sometimes only observed under specific ecological conditions.

Invasion, establishment and spread

Release of transgenic fish into the environment, either deliberately or through escape, opens a further set of issues to be addressed. One must take into account dispersal behaviour, fitness components of the fish

(e.g. survival, fertility, viability) and introgression and gene flow into related populations (both intra-specific and inter-specific). In addition, bottleneck effects and outbreeding depression are possible side-effects of the introduced transgenic fish on wild populations in the receiving environment.

A classic scientific approach to fitness would take into account all the components of fitness such as fertility, growth, and behaviour. We have to be aware that pleiotropy (i.e. one genetic factor resulting in more than one effect) makes the classical approach more complex. An alternative approach is the "net fitness" approach where we don't need to know everything about a fish, but we just measure the global fitness of the fish (i.e. the number of offspring produced). Net fitness is difficult to test for in nature, as it is a long-term measurement taken over a sometimes large geographical area. It was instead proposed to measure net fitness in a near-nature environment such as laboratory tanks set up to mimic a natural setting.

Containment and other management strategies

Containment is one type of management strategy which provides the most control over transgenic fish. This may be achieved through physical approaches such as land-based growing facilities or improved net pens, or through biological approaches. Biological approaches include sterility via triploidy or transgenic approaches, or impaired viability through engineered dependence on an introduced nutrient source. When containment is not possible, mitigation of issues in environmental release must be considered, and includes use of, for example, detection methods and biomarkers.

Scale of the risk assessment

The scale of risk assessments undertaken depends on several issues including geographical and temporal considerations. Geographical considerations include connectivity of waterways and specificities of aquatic ecosystems. For example, freshwater habitats are particular environments which may be more vulnerable to invasions. Temporal considerations include the life stage of the fish released and whether the fish are sterile, with a limited lifespan, or are able to reproduce through successive generations. The magnitude of the release, whether deliberate or an escape, and the total number of animals must also be considered.

Methodological needs

In order to carry out adequate environmental risk assessments on transgenic fish, collection of basic biological data on fish species, including their ecological niches and local genotypes, is a critical first step in collecting baseline data. Case studies using reference species (e.g. salmon, tilapia) may help to elucidate effective scientific approaches to data gathering. Suitable experimental designs, ideally mimicking conditions in nature, would help in the development of protocols for risk assessment.

It was noted that more empirical data is needed for modeling studies. Models can take several forms: logical models are qualitative, mathematical models are predictive and quantitative, and models of interactions focus on the synergies and antagonisms. Components of the model may include population density, genetic diversity, life history parameters and abiotic factors. Studies will reveal interactions between factors and an analysis of the variability of factors leading to sensitivity analysis.

Special attention should be paid to the identification of critical life stages and critical environmental variables and fitness components. These critical points can be identified from a combination of modeling approaches and experimental data. Simulation and predictive models cannot fully replace experimental approaches to scientific data gathering. Indeed, modeling provides indicators as to the types of experiments which will yield the most useful data. Modeling, laboratory experimentation and

observations in nature are synergistic components of the comprehensive scientific assessment and should be implemented in parallel.

Additional Considerations

The following issues were also brought up in the discussions but were not further elucidated because the main focus of the session was on science-based environmental risk assessment: Balance and weight of evidence evaluation, including quantitative data and qualitative observations (expert opinions); degree of uncertainty in scientific data, human health aspects e.g. fish as food; and socio-economic aspects.

3. Recommendations for Additional Research and Specific Data Needs

Some research needs were identified, and although the list below is not exhaustive it represents the points which were most highlighted by the participants of the transgenic fish session.

- Method development needs are compiled in the paragraphs above.
- Develop different worldwide scenarios on the introduction of transgenic fish into the environment by a group of experts in, for example, ecosystems, fish physiology and fish genetics.
- Perform sensitivity analysis in models to identify critical life stages, fitness components or environmental variables for which we do not yet have any experimental data.
- Identify other likely candidate model fish for use in case studies for environmental risk assessment.
- Development of case-by-case protocols for transgenic fish risk assessment.

4. Available risk assessments and guidelines

- Biology of Atlantic Salmon, a draft developed by the OECD working group on harmonization of regulatory oversight in biotechnology, 2007
- Global Industry Coalition (GIC) compilation of environmental risk assessment guidance: transgenic animals (including fish), 2007
- Canada Department of Fisheries and Oceans workshop output from 2004 on environmental risk assessment of GM fish
- *Codex Alimentarius* Commission task force on food safety of genetically modified animals
- Abstracts of the OECD workshop on the biology of the Atlantic Salmon, Moscow, Russian Federation, 2004.

Transgenic trees Session

Chair: Bao-Rong Lu

Dr. Bao-Rong Lu set the scene for the discussion by highlighting the differences displayed by trees compared to annual crop plants: they can grow in unmanaged conditions, have a long life expectancy, are broadly undomesticated. Dr. Lu then presented the objectives for the discussion: to identify what is known, what new knowledge is required specifically for trees; based on scientific facts, avoiding policy issues.
Dr. Meng-Zhu Lu shared his experience and knowledge gained over almost 10 years with poplar (P. nigra) transformed with a Bt gene for insect tolerance, and with a white poplar hybrid transformed with a

Bt gene and a proteinase inhibitor gene. Dr. Lu presented the gradual steps involved (laboratory bioassays, small scale field release, commercialization); the steps of government oversight; the general location and climatic conditions of the growing sites; and the risk assessment parameters assessed over one year: toxicity, gene stability; effect on soil microorganisms; effect on insect populations; gene flow (pollen and seed).

Adequate Framework in the Protocol

An important point that was consistently raised is that the general principles and methodologies as described in Annex III of the Cartagena Protocol also cover trees. The framework for risk assessment offered by the CBD can therefore be used to address specific issues raised by trees. The way these issues are addressed for trees may be specific, but the assessment framework remains the same and no new paradigm is required.

Specific characteristics of trees

Specific characteristics of trees were outlined: perennial, large population size, often many years before the first flowering, complex ecological backgrounds; huge range of domestication, from non-domesticated (forest trees) to highly managed (stone fruit); trees are perennials and release may be over the long-term; trees are often the dominant species in the environment; wind pollinated trees produce large amounts of pollen some of which can potentially travel long distances; some trees are potentially vulnerable species; there can be issues related to plantations themselves compared to natural regeneration; requirement for a deployment strategy involving several genotypes. It was consistently noted that forest species that may have large wild stands in close proximity to cultivated stands, and fruit trees that are highly bred and manipulated for sterility, fruit quality, disease resistance etc. for many years, raise very different issues.

Key issues

The considerations to be taken into account in any risk assessment of living modified organisms according to the Cartagena Protocol are also important in the risk assessment of transgenic trees: gene stability; interactions with microorganisms; non target effects; gene flow – distances traveled by pollen of wind pollinated species and tree populations connected over large areas; evolution of insect resistance; allergenicity issues; fitness and long-term food web effects.

Comparator/counterpart

To evaluate the relative magnitude of effects in the environment, one approach of risk assessment is to compare the effects with trees produced by conventional breeding that we are familiar with. A key component in risk assessment is what you compare the transgenic tree to, in terms of the composition, phenotypic and agronomic/forestry aspects. In the need to look at a comparator, management systems must also be considered (e.g. use of herbicides, insecticides, defoliators etc.); do not look at transgenic trees in isolation.

Baseline information

To evaluate the relative magnitude of effects in the environment, one must have a realistic understanding of the state of the environment before the introduction of these trees. The assessment and evaluation of indirect effects in the context of food webs require strong baseline knowledge, that is currently lacking for semi-domesticated and unmanaged systems. More modeling systems would be helpful to inform decisions.

Case by case assessments

Participants consistently agreed that a case by case approach to the evaluations was extremely important, using the existing framework. There was discussion over what a case by case assessment really means. Suggestions were to categorize the risks (biodiversity, gene flow, non targets, resistance evolution issue); categorize the genes (such as "neutral" genes, lignin properties modification, hormone regulation, etc.); categorize the species (dominant species in unmanaged ecosystems, species that require human intervention for survival, etc.). There was no general agreement on the definition of a case, e.g. event-based case by case assessments. To facilitate risk assessment it should be identified to what extent classes of genes can be considered safe in a given species and ecosystem. Interestingly, a comment was made that what is case by case will be determined on a case by case basis; it will be different in each case depending on familiarity. You can go from very specific to broader and broader as you gain familiarity, using the same principles as with crop plants.

Field trials

A key consideration in gathering the necessary scientific data is the way the field trials are conducted. Genotype by environment interactions are a key consideration. Field trials are important for risk assessment work together with baseline information. Reliable answers to some questions will only be obtained with field trials including flowering. For trees, greenhouse trials are more limited, therefore relevant data needs to be gathered from open field trials. Testing in the field needs to be over several years and often in several locations, due to strong potential weather variations from year to year and important genotype by environment interactions that will affect fitness and reproductive fitness. Some participants recognized that moving to field trials and flowering trees did pose concerns especially with regard to monitoring gene flow to either other populations of the same species or to wild relatives. Article 16 (4) of the Protocol states that each Party shall endeavour to ensure that any living modified organism has undergone an appropriate period of observation that is commensurate with its life-cycle or generation time before it is put to its intended use. Decisions will need to consider the risks and benefits in the future developments.

Biological containment

Male and female sterility are interesting candidates for containment, provided potential pleiotropic effects are considered. Effective biological containment technology may be important Many of the biological containment methods may involve genetic modifications and will therefore themselves also be subject to risk assessment. It is also important to combine the risk assessment with risk management measures.

Fitness

Fitness (both increased and decreased) was discussed extensively as a key component of risk assessment, especially if there is introgression into wild populations. This was seen as a very challenging area to study, with ambient conditions changing over time that make it difficult to identify local fitness over the long-term. The concept of relative fitness and absolute fitness was presented. The issue of spread of alleles is a question of relative fitness; but if there are concerns about a species becoming weedy or invasive in the environment, absolute fitness is important. Fitness changes across genetic background and environment, and conditions change over the years (increasingly so with global change and the introduction of exotic pests and diseases). These issues can be considered by using modeling approaches. A weakening fitness integrated into wild populations was seen as an important risk to consider, while increased fitness might lead to changes in invasiveness. If there is no introgression into wild species, such as in some fruit trees, then estimating relative fitness would be inappropriate. Some participants recognized that it is important to identify high risk cases that should not be used. Some participants raised

the special case of restoration of ecosystems (e.g. chestnut, English elm) as an example where gene flow to natural populations would be encouraged.

Centres of origin

In centres of biodiversity and origin extra caution may be required (ex. eucalyptus in Australia), and some indicated that experiments and releases should be avoided

Available knowledge

There is a wealth of experimental information on breeding developed for the past 50 years. The European Advisory Committees on biosafety met in Ljubljana half a month ago to discuss deliberate release of GMOs. The final report from that meeting is expected soon*. The United States Department of Agriculture (USDA-APHIS) has carried out 12 environmental assessments for field trials of transgenic trees, and also assessed and deregulated 1 type of fruit tree; virus resistant papaya; the OECD has produced biology documents that have a wealth of information for tree species. The OECD also organized a workshop on transgenic trees in 1997 with clear recommendations that need to be taken into consideration. The National Academy of Sciences has issued a chapter on tree confinement systems in their 2004 Report on biological confinement†. The Advisory Committee on Releases to the Environment (ACRE) in the United Kingdom has produced a document on Management of Footprint of Agriculture‡.

Knowledge gaps

- How to properly measure fitness for risk assessment
- To have effective risk assessment in a timely fashion
- Define case in a correct way, by use, by product in a proper and transparent manner
- Pleiotropic effects
- Genotype by environment interactions
- Study of mychorrhizae and other interacting microflora

Recommendations

- Treat trees in the managed and wild habitats differently
- How to produce effective risk assessment for trees in a timely fashion given the life cycle of trees
- Effective measurement of fitness suitable for trees

Pharmaplants Session

Chair: Dr. Moisés Burachik

1. Scope of the Session

Discussions on environmental risk assessment on pharmaplants were opened by the Chair by inviting participants to identify key issues of discussion. Agreement was reached to limit the discussion to plants producing therapeutics, diagnostics and vaccines, notwithstanding that there are related risk assessment issues with other modified plants for the production of industrials, diagnostics, nutraceuticals, etc.

* http://www.mop.gov.si/en/areas_of_work/environment_directorate/sektor_za_biotehnologijo/2nd_meeting_of_euro

† http://www.nap.edu/books/0309090857/html/

‡ http://www.defra.gov.uk/environment/acre/fsewiderissues/pdf/acre-wi-final.pdf

There was additional discussion related to linkages between risk assessment and risk management. It was agreed that the distinction between assessment and management is not always clear in the context of pharmaplants.

2. Issues to take into consideration for the Risk Assessment

It was recognized that the general principles and methodologies as described in Annex III of the Cartagena Protocol also cover issues relevant to pharmaplants. This will include, for instance, biology data of the plant, gene expression levels, tissue specificity and timing of the expression, etc. The framework for risk assessment offered by the Cartagena Protocol can therefore be used to address specific issues raised by pharmaplants. The following areas were discussed:

i. No special restrictions to date have been generally agreed to concerning plants that should not be used for the production of pharmaceutical products. However, Mexico has restricted the use of maize for pharmaplants. It was recognized that the use of crop plants may pose a risk of the pharma protein entering the food chain in case of inadvertent release into the environment and this consideration may also play a critical role in risk assessment. On the other hand, plant species which are not commonly used as food/feed sources are often less known with regard to relevant biological properties, such as fitness, degree of domestication, weediness, dormancy, dispersal, persistence in the environment. This last point was identified as a relevant knowledge gap in the development of a pharmaplant industry. Therefore, some participants proposed that a set of criteria for the selection of the appropriate plant species, on a case-by-case basis, should be considered.
ii. As expression levels of the protein of interest will generally be higher in pharmaplants compared to first generation genetically modified plants, the issue of potential toxicity to non-target organisms may need to be considered and appropriate panels of non-target organisms may be useful to consider. Similarly, worker safety/human exposure to the relevant protein(s), during harvest and processing, for example, may require appropriate assessment of toxicity, allergenicity, and other potential health effects. Where appropriate, attention should be paid to chronic low-dose effects of the compounds on the reactivity of the immune system and its susceptibility.
iii. Persistence in the environment, as well as mechanisms for protein degradation and derived products, may also be considered. Also, environmental degradation of the pharmaceutical protein versus its persistence in the environment should be distinguished with supporting data.
iv. When appropriate, gene stability should be included in the risk assessment and followed up during monitoring and risk management.
v. Release into the environment of the plant or plant part(s) may require consideration of the biological activity and in addition the oral acitivity of the protein being produced. For example, a host animal consuming a monoclonal antibody will have different consequences compared to the consumption of an antigen against a feed-borne disease.
vi. Special attention may need to be given to the possibility of gene flow to wild relatives in the context of non-target effects and overall biodiversity effects.
vii. The level of expression/dose relationship and lot to lot variations were also identified as risk assessment issues.
viii. Several participants recognized that the high expression of the pharmaceutical product itself may have phenotypic effects on the plant in addition to expression of other auxiliary genes introduced in the construct. Supporting data relevant to the risk assessment should be included in the application.

ix. Certain risk assessment data for pharmaplants would be similar to the information requirement for genetically modified crop plants, in general. However, it was identified by some participants that for some pharmaplants, the comparator in the risk assessment may not necessarily be the non-modified plant species (as it is used in current genetically modified crop plant species), because it is not intended to be used as a food/feed source, but the production of a specific pharmaceutical protein. However, when evaluating effects on natural biota, agriculture may be the appropriate comparator.

3. Issues to take into consideration for the Risk Management

Since it is recognized that the distinction between risk assessment and risk management in the context of pharmaplants is not always clear, participants discussed the following issues as appropriate components of a risk management framework:

i. Scale of production: Safeguard measures employed in qualitative and quantitative terms (e.g., redundant, overlapping confinement/containment measures) will vary depending on scale.
ii. Confinement/containment measures: Every possible route and level of exposure (e.g., to rodents, insects, and other non-target organisms) may have to be considered when designing confinement/containment measures to minimize exposure of the pharmaplants to the environment. Appropriate systems of confinement are to be determined on a case-by-case basis, considering the plant, climate conditions and the product being synthesized. Efficacy of confinement measures are important to consider inter alia in relation to extreme weather conditions.
iii. Good manufacturing practices (GMP): Careful design of standard operating procedures, detailed registration of all operations, traceability and accountability of materials, validation of methods, continued training of personnel and strict biosafety measures were considered important elements of GMP in the case of pharmaplants intended to be processed to obtain the active product.
iv. Consumption/unauthorized use: Special measures should be implemented to prevent unauthorized use or.direct consumption of the plant. Availability may need to be strictly controlled.

4. Conclusion

While a number of general risk assessment elements apply equally to pharmaplants and non-pharmaplants, there are certain special characteristics for pharmaplants that may require additional risk management approaches necessary to prevent or reduce the risks to biodiversity and consider risks to human health. It was recognized that most of these issues can be addressed with available methodologies.

In particular, knowledge gaps were found, including in the following areas:

- The process by which pharmaplant products inadvertently enter the food/feed chain
- The phenotypic and pleiotropic effects of high levels of newly expressed proteins
- The potential effects of different and novel exposure routes of pharmaplants or their products to human, animal and non-target organisms, including impact on foodwebs
- The potential for occupational hazards
- The handling of pharmaplants when the intended use is their direct consumption
- The potential impact of disposal of pharmaplants into the environment
- The efficacy of containment measures when transferred to different country contexts.

GM Viruses for Management of Animal Populations

Chair: Helmut Gaugitsch (Austria)

1. Summary of Session

Discussion in the group followed the structure of the background document on GM viruses. Contents and recommendations of the background document as well as the presentation in the plenary on the subject were generally endorsed by the participants. The Group focused its discussion on environmental applications of GM viruses for management of animal populations but also took into account human, livestock and wildlife health considerations where appropriate.

2. Current state of the art / available science

While there is some experience with 'intended' releases of viruses, it is necessary to also look at experience from other sources including animal and human disease epidemics and from data arising from vaccination programs (the examples of small pox and adenovirus were given). Two categories of possible application were identified: vaccination against human and livestock diseases and vaccination of wild species. In the first case, non-replicating vectors are preferable from a safety perspective while in the second case, replicating vectors would be needed.

Several participants expressed the view that viruses are different from most other micro-organisms with respect to transboundary movement, persistence/latency, infectous processes and basis for host preferences. They were also of the view that viruses are biologically unique in other respects as well, e.g. frequency of mutation, recombination and horizontal gene transfer.

We should also consider experiences from cultures in which there is a close relationship between humans and animals (regarding viral transmission across species barriers).

There is very little data or information on environmental effects of GM viruses for management of animal populations; previous focus has been on human or animal health only. For example, biological control of rabbits in Australia was partially effective in controlling their population but with little study of virus ecology that included interactions between introduced and natural strains, and there was little in the way of measuring possible environmental effects. Other examples with foxes and mice were not further pursued because of doubts regarding host specificity and efficacy. Recombinant rabies vaccines are used in baits in Europe and North America; again environmental monitoring of effects was limited.

It was mentioned that food safety work undertaken under the Food and Agriculture Organisation (FAO)/World Health Organisation (WHO) *Codex Alimentarius* taskforce as well as the World Organisation for Animal Health (OIE), may be useful in the environmental context.

3. Available guidance and risk assessments including research

In general, such guidance for environmental effects of release of viruses (e.g. non-target effects) is either non-existent or limited. Some international bodies, such as OIE, *Codex Alimentarius*, EMEA, WHO provide partial guidance by focussing on clinical aspects. For example, some issues like viral shedding to the environment will have relevance for both clinical and environmental assessment.

New analytical methods such as meta-genomics, and bioinformatics, when validated, offer a means to measure and assess viral diversity and effects in the environment.

It was suggested to put risk assessment into context with social and economic considerations, but implementation was not discussed. The need for co-ordinating the work of different organizations in this

area was recognized. Risk assessment should be complemented by meaningful monitoring and surveillance programs.

There are only a few examples of research underway in this area.

4. Summary points based on discussion on gaps

There is minimal knowledge of biology of viruses concerning ecological interactions and therefore there is a need for:

- developing consensus documents summarizing the existing body of knowledge e.g. vaccinia, adenovirus
- identifying groups of viruses according to their use
- developing or using existing international databases (e.g. relevant academic databases, international virology databases, Biosafety Clearing House, Biosafety Information Resources Centre)

In addition, there is minimal knowledge of indigenous viruses (in the environment of intended introduction), in which case existing viruses, possibly also including plant viruses, may be a source of possible recombination. In cases where regulatory decisions have been made, the BCH or other databases could be used to fill that gap. Also, there is minimal knowledge of virus/host interactions (e.g. host range, co-evolution, cytopathogenicity). Therefore a tiered, case-by-case approach, e.g. laboratory studies followed by animal studies and/or field studies should be followed. In order to allow for a comparative assessment such an approach should be used for both wild type and modified viruses. Caution was however raised concerning extrapolation from laboratory experiments to field situations.

It was pointed out that techniques have become available, e.g. quantitative PCR-based techniques and DNA-chip hybridization techniques, that will make more detailed assessment of field situations possible in a cost-effective way.

Models for integration and generation of information for risk assessment can be used where available and validated but confidence in them is dependent on base-line knowledge and existing animal management systems. Epidemiological models may be particularly helpful.

Where there have been releases, lack of follow-up / monitoring or surveillance data is an issue.

Finally it was recommended that international co-ordination and collaboration be encouraged within existing organizations. The Convention on Biological Diversity or OIE could play a role here. This could include encouraging research and capacity building (North / South collaboration) and multi-disiplinary themes.

C: Recommendations of the workshop

- The general principles and methodologies for risk assessment contained in Annex III to the Cartagena Protocol also apply to transgenic fish, trees, viruses and pharmaplants.

- There is insufficient guidance on how to perform risk assessment for GM fish and viruses.

- There may be a need to develop specific methodologies and specific protocols for generating data necessary to conduct risk assessments for the future applications of modern biotechnology, especially for transgenic fish, trees and viruses.

- All risk assessments of living modified organisms should be conducted on a case-by-case basis as the impacts depend upon the trait inserted, the recipient organism and the environment into which it is released.

- There is a need for additional data on several elements necessary to conduct risk assessments for all four types of transgenic organisms (fish, trees, viruses and pharmaplants). Further research is recommended to fill the knowledge gaps, inter alia the specific gaps identified during the workshop.

- Field trials may be a useful tool to generate data on the impacts of living modified organisms, but may give raise to particular concerns. Alternative models for generating data, as well as containment and confinement measures should be considered when appropriate. Baseline information on the specific organism in question is very important for risk assessments.

- There is value in considering the differences between highly managed systems such as cultivated fruit trees and the more variable cases such as some forest systems and animal wildlife, and whether the recipient organisms are domesticated, semi-domesticated or non-domesticated species.

- Existing guidelines, methodologies, baseline information and risk assessments should be made readily available through the Biosafety Clearing House and other relevant international databases.

Annex I

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