



Annual Report

International Scientific Association for Probiotics and Prebiotics

January 1 – December 31, 2004

Contents

Introduction

2004 Board of Directors

2004 Accomplishments

2005 Objectives

Appendix A: ISAPP Quality Control Network

Appendix B: Report on European Food Safety Authority meeting in Brussels 2004

Introduction

ISAPP is an international non-profit collaboration of scientists dedicated to advancing the science of probiotics and prebiotics. The mission statement of ISAPP is: To engender and disseminate information on high quality, multidisciplinary, scientific investigation in the fields of probiotics and prebiotics, and to advance the development of scientifically substantiated, health-promoting probiotic and prebiotic products worldwide. ISAPP is the only scientific organization dedicated specifically to probiotics and prebiotics, bringing together scientists from all pertinent disciplines, including food science, microbiology, immunology, biochemistry, nutrition, molecular biology and medicine. As a scientific society, ISAPP strives to have all activities focused on science, not the promotion of any specific commercial products.

For additional details, see website www.isapp.net

Message from the President

The year 2004 was an especially exciting year, as I was able to serve as President of ISAPP and also local host for the annual meeting.

Challenges to the probiotic and prebiotic fields continue. With a backdrop of increasing numbers and quality of studies on probiotics and prebiotics, the quality of commercial products has met with criticism in the scientific literature and in the popular press. Fourteen peer-reviewed papers have been published which evaluate commercial probiotic-containing products. All conclude that many commercial products do not adequately meet label claims. However, in some cases, these conclusions are derived from questionable methods. Solutions to this problem are not straightforward and would require tremendous resources and commitment from commercial entities. See Appendix A for an ambitious proposal for an ISAPP-sponsored testing laboratory suggested by Bruno Pot. What would be involved in establishing a testing laboratory was discussed at our 2004 IAC meeting, but such an endeavor was thought to be beyond ISAPP's current resources. The problem still remains, however, and will likely need to be more fully addressed as this field progresses.

Of continued importance to the field of probiotics is the lack of regulatory definition of the term "probiotic". Although the scientific definition is clear, the term continues to be used on products



that do not meet the minimum criteria of a probiotic – live microbe administered in an adequate dose with a documented health effect in humans. The term should be applied only to the specific strains which meet these criteria, not to entire genera or species. As the field continues to expand, indiscriminate and inappropriate use of this term will serve only to erode consumer confidence.

I would like to extend a heartfelt thanks to the 20 companies who provided financial support to ISAPP during this year, to the Board of Directors, whose scientific and organizational advice paved the way for ISAPP's progress and to the scientific delegates who attended the ISAPP meeting and were critical to providing the sparks of intellectual debate and networking opportunities that allow the benefits of ISAPP activities to translate into scientific progress for the field.

A handwritten signature in cursive script that reads "Mary Ellen Sanders".

Signed: Mary Ellen Sanders



2004 Board of Directors

There were no changes from 2003 to the Board of Directors.

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2004 Accomplishments

- **2004 ISAPP Annual Meeting.**

ISAPP met for the 3rd time to discuss the latest scientific developments in probiotics and prebiotics. This by-invitation meeting, surrounded by the grandeur of the Rocky Mountains in Copper Mountain Colorado August 29-31, 2004, convened 84 invited scientists from 13 countries. Presentations by Joel Weinstock (University of Iowa), Thadeus Stappenbeck (Washington University School of Medicine), Connie Weaver (Purdue University), Ian Rowland (Northern Ireland Centre for Food and Health) and Peter Lee (Stanford University) covered a range of topics from use of helminthes to modulate immune dysregulation to probiotics bioengineered to improve resistance to HIV. Discussion sub-groups were convened for a full day on the topics of Engineered probiotics as therapeutics: formats and challenges; Host commensal interactions - who talks to whom and how; Omics technologies - exploration of the interaction of pro and prebiotics with the host; Hygiene and immune regulation; Biomarkers for healthy people; Prebiotic and probiotic applications to companion animals; Development of a probiotic dossier using science-based criteria and Physiological relevance of prebiotic activity. The complete scientific program and press release can be downloaded at www.isapp.net.

A report from the 2004 meeting was prepared and submitted for publication to Current Issues Intestinal Microbiology (Sanders, ME, Guarner, F, Mills, D, Pot, B, Rafter, J, Rastall, R, Reid, G, Ringel, Y, Rowland, I, Saarela, M, and Tuohy, K. Selected Topics in Probiotics and Prebiotics: Meeting Report for the 2004 International Scientific Association for Probiotics and Prebiotics).

In addition to the academic participants, about 25 industry scientists participated in the meeting. Twenty companies committed to science-driven probiotic and prebiotic product development contributed financially and scientifically to the meeting. Most companies are members of the ISAPP Industry Advisory Committee. This body interacts closely with the ISAPP Board of Directors, identifying key scientific issues important to the advancement of this field.

- **2004 Industry Advisory Committee Meeting**

Industry contributors to the 2004 ISAPP meeting were Biogaia, Chr. Hansens , Dairy Management Inc., Danisco, Danone, Fonterra, General Mills, Hills Pet Nutrition, Institut Rosell, Mead Johnson, Nestle, Orafiti, Procter & Gamble, Rhodia, Wyeth, Bradley Pharmaceutical, California Dairy Research Foundation, Genencor, Genova Diagnostics, and VRI.

- **ISAPP Considered Issues in Probiotics and Prebiotics**

ISAPP Considered Issues in Probiotics and Prebiotics concept was launched, with a commissioned article from Dr. David Mack on the safety of L-lactic acid producing probiotics. The article was published in the Canadian Journal of Gastroenterology (18:671-75, 2004).

- **List of ISAPP Publications to date**

- Tompkins TA, Sanders ME. 2004. Good intentions, poor study design. Can Fam Physician. 50:1499-500.
- Mack D. 2004. D(-)-lactic acid producing probiotics, d(-)-lactic acidosis and infants. Canadian J Gastroenterol. 18:671-5.



- Reid G, Guarner F, Gibson G, Tompkins T, Gill H, Rowland I, Rastall B, Pot B, Sanders ME. 2004. Discussion on toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. *Gastroenterology*. 127:366-7.
- Reid G., Sanders ME, Gaskins HR, Gibson GR, Mercenier A, Rastall R, Roberfroid M, Rowland I, Cherbut C, Klaenhammer T R. 2003. New scientific paradigms for probiotics and prebiotics. *J Clin Gastroenterol*. 37:105-118.
- Ferber D. 2002. Much ferment on the probiotics front. *ASM News*. 68:369-370.
- **Website.** The www.isapp.net website is still managed by WS Design and continues to be the key means of communication with ISAPP delegates.
- **2004 Meetings of the Board of Directors**
 - August 28 and August 31, 2004 at Copper Mountain, Colorado.
- **Heimbach report to ISAPP on European Food Safety Authority meeting in Brussels**

The European Food Safety Authority convened a session in Brussels, Belgium, 13-14 December 2004, to discuss “Scientific Colloquium on Microorganisms in Food and Feed: Qualified Presumption of Safety”. Jim Heimbach (JHeimbach LLC JHeimbach@aol.com) attended on behalf of ISAPP and filed a report (Appendix B).
- **2005 Objectives**
 - ISAPP will focus in 2005 on expanding our sphere of influence into other geographical regions and partnering with significant scientific organizations with compatible goals with ISAPP.
 - Continue to explore ways the IAC companies can get an adequate return on their investment in ISAPP.

Appendix A. ISAPP Quality Control Network

Topic for the agenda for the IAC meeting: ISAPP Quality Control Network

Presented by Bruno Pot

State of the Art

Despite existing initiatives (Table 1), problems related to the quality of analysis of commercial probiotic-containing products abound. Fourteen peer-reviewed papers have been published (Table 2) evaluating commercial probiotic-containing products. All conclude that commercial products do not adequately meet label claims. Some come to this conclusion from results generated by questionable methods.

Table 1. Efforts relevant to establishing standards for probiotic bacteria in commercial products

Organization	Region of Impact	Action
Food Agriculture Organization/World Health Organization (www.fao.org)	Worldwide	Developed guidelines for the Evaluation of Probiotics in Food
International Dairy Federation (www.fil-idf.org)	Worldwide	Established a Joint Action Team on establishing methods to determine certain functional and safety properties of probiotics in food, as stipulated in the FAO guidelines for the evaluation of probiotics in food
European Food & Feed Culture Association (www.effca.com/anglais/pages/id_links.htm)	Europe	Developed guidelines for use of probiotics in foods
Codex Standard for Fermented Milks (Codex Stan 243-2003) (http://www.codexalimentarius.net/more_info.asp?id_sta=400)	Worldwide	Among other composition stipulations, this standard specifies minimum numbers of characterizing and additional labeled microbes in yogurt, acidophilus milk, kefir, kumys and other fermented milks
National Yogurt Association (www.aboutyogurt.com)	US	Petition under consideration by the FDA which would change the standard of identity of yogurt, including requiring minimum levels of live cultures in yogurt, but not specifically levels for any additional probiotic cultures

In many cases this is due to (i) the lack of proper certified laboratory networks that can perform these quality control evaluations in a reproducible and certified way, (ii) the lack of proper reference materials, and possibly due to (iii) the lack of goodwill of some of the producers of



probiotic products to deposit their isolates and/or their isolation procedures in independent certified central depositories.

Therefore the idea was raised (by industry and by ISAPP board members) to explore if ISAPP could play a mediator role in setting up a proper infrastructure to match these needs.

ISAPP's involvement could be peripheral (perhaps as a springboard to get a more international buy in to the effort). However, what is not needed is to simply provide yet another analysis protocol. ISAPP must be very practical, directing efforts to the creation of an actual functional network for testing of strains and products, with balanced distribution of laboratories in N. America, S. America, Europe and Asia.

Possible solution / activity

- Assemble world-wide a number of expert laboratories which contribute with protocols and analysis power in their specific field(s). Make sure to have duplicate expertise in the N. & S. Americas, Europe, and Asia.
- Decide on specific protocols for specific quality control tests; if necessary for legal or efficacy reasons, let industries provide adapted protocols themselves.
- Arrange confidentiality agreements with these labs.
- Distribute protocols to laboratories involved.
- Organize a training procedure and / or session at a single laboratory to improve reproducibility and exchangeability of test results.
- Organize regular 'examinations' on artificial (anonymous) samples (every six months) as a basis for certification.

This procedure can be compared to e.g. the PulseNet initiative in the US for foodborne pathogens, <http://www.cdc.gov/pulsenet/>, which is using standard protocols, with regular training and exams of technical staff, with a uniform database and with regular validation of methods on reference samples (the approach even made it to a 'mission critical application' in the USA).

- Provide laboratories with proper reference systems and tools to compare / calibrate results.

Possible ISAPP role

Setting this up could theoretically be an ISAPP activity:

- Define role of ISAPP exactly (e.g., would ISAPP have final legal responsibility of the results?)
- Fix a clear strategy for action
- Define experts in this field, academic, regulatory, industry and members of interested/active organizations (IDF, EFFCA, etc)
- Develop / decide standard protocols
- Decide on candidate laboratories
- Mediate protocol transfers
- Set-up control structures (act as certifying organization).
- Develop a uniform database, with regular validation of methods on reference samples
- Develop a depository of reference strains and product information / labels
- Make sure it is an INTERNATIONAL organization.
- Solicit contribution of industry and public organizations



- Organize practical analysis of products by acting as mediator between industry and laboratories (e.g. guaranteeing anonymity if necessary; see also below).
- Organize possible research for further protocol optimization / relieve of bottlenecks.
- In collaboration with the analysis labs: seek (additional) financing at official organizations (IDF, NIH, EU, others) to finance e.g. additional research activities.

Initial steps (for Colorado):

- Circulate this draft to board members to determine how they see this issue
- Circulate this (or modified draft) among session 7 members (and other interested people) to determine how they see proceeding
- Develop an agenda
- Find out if industry is willing to contribute to the general maintenance of such an infrastructure, e.g. by paying for these routine analyses by setting up a meeting in Colorado where this issue is moved into a working group subcommittee with a short introduction at the general IAC meeting (composition, see below).

Industry role

- Financing the network through orders and deposits
- Safe deposit potential for their strains and protocols.
- Confidential analysis of their products in a standardized way (technical-, safety-, functional aspects).
- Situating their products in a vast reference scheme (represented with anonymous strains / products).
- Possibility to 'advertise' e.g. 'counts certified by institute XXX'; elimination of cowboys.
- Assistance in publications (marketing or scientific).

Benefit for society

Initiative open to consumer organizations, quality control organizations, governments, etc:

- Validation of content of probiotic products - do they have what they say they have through the end of shelf life? Raising consumer confidence.
- Eliminate (minimize) future publications on 'surveys' of commercial products, using un-validated methods, and sometimes arriving at erroneous conclusions
- Contribute to new legislation development.

Composition of the IAC committee working group

Need people who are committed and who will do their homework:

- Member(s) of the board of ISAPP (Bruno Pot)
- Representative from EFFCA
- Representative from WHO / FAO
- Representative from PulseNet
- Representative from IDF Joint Action
- Representative from Europe industry
- Representative from S. American industry
- Representative from ASIA industry
- Representatives from N. American industry

Table 1. Studies of content of commercial probiotic products available to human consumers

Products tested	Results	Methods Used	Reference
20 lactobacillus supplements, some blended with bifidobacteria	1 of 20 contained microbes consistent with product label	16S rDNA sequencing; no enumeration of levels	Berman and Spicer 2003
8 dried 'L. acidophilus' supplements	10 ⁵ or less lactobacilli/g in 4 products 3 contained L. acidophilus	Plate count Carbohydrate fermentation	Brennan et al. 1983
15 supplements	8 were accurately labeled for species; 1 contained labeled levels of all bacteria;	Selective plating Carbohydrate fermentation	Canganella et al. 1997
9 South African supplements	3 of 9 products contained labeled bacteria;	Selective plate count DGGE	Elliot and Teversham 2004
13 dry, liquid or milk products claiming 'L. acidophilus'	3 contained <i>L. acidophilus</i> ; 6 contained bile tolerant lactobacilli >10 ⁶ /g or ml	Selective plate count with oxgall	Gilliland and Speck 1977
13 UK supplements	2 of 13 met label claim for species and level; 8 of 13 >1 log below label claim for count;	Selective plating API rapid ID kits	Hamilton-Miller et al., 1996
52 supplement or food products	4 of 11 yogurts declared specific microbes in product, others provided only general descriptors; No mislabeling found in yogurts; 12 of 29 UK supplements content and levels OK;	API rapid ID kits Selective plating	Hamilton-Miller et al., 1999
10 Canadian lactobacillus supplements	0 of 10 matched label specifications	Semi quantitative streak method on blood agar	Huff 2004
			Hughes and Hillier 1990
4 brands Australian probiotic yogurt in full and reduced fat with L. acidophilus (3 also contained bifidobacteria)	<i>L. acidophilus</i> levels varied widely between products (<10 ³ – 10 ⁸ /g); 1 of 4 brands had <10 ³ /g bifidobacteria	Selective plate count Tested stability over 6 week storage	Micanel et al. 1997
50 Australian yogurts with bifidobacteria and L. acidophilus	>10 ⁶ <i>L. acidophilus</i> in 24% >10 ⁶ bifidobacteria in 14%	Selective plate count	Rybka and Fleet 1997
10 products (4 dairy, 1 juice, 5 dried)	4 did not contain all claimed species (DNA-based analysis)	DNA-based, culture independent analysis, DGGE; Culture enrichment;	Temmerman et al. 2003
55 European probiotic products (30 dried supplements; 25 dairy products)	11 of 30 supplements contained no detectable microbes; 6 of 55 products contained all claimed microbes;	Selective plate counts	Temmerman et al. 2003
5 supplements	3 of 5 met label claim for	Selective plate	Weese 2002

	species and 2 met claim for levels;	counts	
6 dairy products	3 of 6 products were correctly labeled with bifidobacteria	Carbohydrate fermentation study Microtiter Colorimetric DNA hybridization	Yaeshima et al., 1996

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7. Hamilton-Miller, J. M. T., S. Shah, and J. T. Winkler. 1999. Public health issues arising from microbiological and labeling quality of foods and supplements containing probiotic microorganisms. Pub. Health Nutr. 2:223-229.
8. Huff BA. 2004. Caveat emptor. "Probiotics" might not be what they seem. Can Fam Physician. 50:583-7.
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14. Weese JS. 2002. Microbiological evaluation of commercial probiotics. JAVMA 220:794-797.
15. Yaeshima T, Takahashi S, Ishibashi N, Shimamura S. 1996. Identification of bifidobacteria from dairy products and evaluation of a microplate hybridization method. Int J Food Microbiol. 30(3):303-13.



Appendix B. Report on European Food Safety Authority Meeting in Brussels 2004

European Food Safety Authority Scientific Colloquium on Microorganisms in Food and Feed: Qualified Presumption of Safety

**Brussels, Belgium
13-14 December 2004**

**A Report to ISAPP by
Jim Heimbach
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Background

The European Food Safety Authority (EFSA) is responsible for providing scientific advice and scientific and technical support to the European Commission with regard to the safety of foodstuffs, food ingredients, and procedures and substances used in the production of foods. A wide variety of bacteria and microfungi are used to produce fermented foods; in many cases, these are well-defined cultures, but many fermented foods are still produced either by spontaneous fermentation or by back-slopping, and the active cultures may be poorly defined.

EFSA notes that these uses of microorganisms are not subject to Community regulation, but rather are presumed to be safe based on their long history of use with no evident harm. However, there is no formal procedure for evaluating and operationalizing this “presumption of safety” such that it could be used as a basis for extrapolation to the likely safety of new applications of these strains and cultures or of closely related strains and cultures.

To this end, EFSA wishes to develop a qualified generic approval system based on the concept of “qualified presumption of safety” (QPS), defined as an assumption based on reasonable evidence and qualified to allow certain restrictions to apply. Such a system would improve the consistency of safety assessment and at the same time make better use of assessment resources by not requiring a full and arguably unnecessary safety review of organisms with a long history of safe use. Case-by-case safety assessments could be eliminated or restricted to only those aspects that are relevant for the organism in question.

EFSA convened a working group consisting of members of the Scientific Committee on Animal Nutrition, the Scientific Committee on Food, and the Scientific Committee on Plants, which prepared a working paper outlining this approach. This paper, *On a Generic Approach to the Safety Assessment of Microorganisms Used in Feed/Food and Feed/Food Production*, is available on the Commission website, http://europa.eu.int/comm/food/fs/sc/scf/out178_en.pdf.

The scientific colloquium was convened with the stated objective “to have an open scientific debate on the QPS approach and to explore options how to develop the concept of QPS into a proposal for the regulatory community that is based on sound scientific principles.” Further information about the objectives and structure of the colloquium may be found at EFSA’s

website,

http://www.efsa.eu.int/science/colloquium_series/no2_qps/610/colloq02_announcement_en1.pdf. Information regarding the results of the colloquium will also be placed on the website later this year.

Process

The colloquium was attended by about 80 scientists from all over Europe, as well as two Americans, Dr. Laura Tarantino of the Food and Drug Administration and me, representing ISAPP. Dr. Tarantino and I were selected to attend because EFSA regards the proposed QPS system as “similar in concept and purpose to the GRAS (Generally Recognized as Safe) definition used in the USA.” Incidentally, we have both concluded that QPS is not in any way similar to the American GRAS approach. While certain uses of substances may be determined to be GRAS based on safe history of use, such history is never regarded as an adequate basis to expand the uses of the substance significantly beyond those already existing.

After a plenary session with an introduction to EFSA and the QPS concept, as well as presentations on the French approach and the American GRAS concept, attendees were assigned to one of four discussion groups for the first afternoon and following morning. The discussion groups were:

Discussion Group 1: Traditional Uses of Microorganisms

Topics:

1. Is the safety evaluation of traditional uses necessary or desirable?
2. If yes, could the QPS approach be adapted to include natural fermentations?
3. If not, how could parameters like the presence of virulence factors and antibiotic resistances be considered?

Discussion Group 2: Taxonomy/Familiarity

Topics

1. What evidence of taxonomic status is needed?
2. What taxonomic level is appropriate for QPS?
3. What happens if a microorganism that has granted QPS would need to be reclassified? Will the QPS status be retained?
4. Is a history of apparent safe use sufficient evidence of safety (and for all purposes)?
5. Is lack of clinical data evidence of a lack of pathogenicity?
6. Should taxonomic units which include pathogenic strains be excluded from QPS?

Discussion Group 3: The Role of Molecular Tools in QPS

Topics

1. What is the role of molecular techniques in taxonomy and strain identification?
2. To what extent do the molecular tools define the risk of transmissible antibiotic resistance?
3. To what extent do the molecular tools define the risk of virulence?
4. What are the issues for the validation of results obtained by molecular techniques?
5. What is the potential of post-genomics tools?

Discussion Group 4: Advantages and Disadvantages of the QPS Approach

Topics

1. What are the strengths and weaknesses of the QPS approach?
2. Are there better alternatives to the QPS approach? If so, what are the advantages and disadvantages of these alternatives when compared to QPS.
3. Should it be a requirement for QPS to deposit the given strain in a culture collection?
4. Could the QPS approach be extended to enzymes and other products of microorganisms?
5. Identify putative consequences of implementing the QPS or any suggested alternatives for e.g. consumers, industry, risk assessors, risk managers.

I requested and received assignment to Discussion Group 4. Incidentally, this discussion group also included two other ISAPP members, Colette Shortt (Yakult) and Eamonn Connolly (BioGaia). The conclusions and recommendations from each discussion group were reported back to a final plenary session for general discussion and conclusions, and the colloquium adjourned.

The plan is for a report of the colloquium to be prepared by the rapporteurs from the four discussion groups. This report will be considered by a newly established EFSA QPS working group charged with revising the QPS working paper, taking into account the comments made and considering how the QPS approach could be applied by EFSA for the safety assessment of microorganisms within the framework of current and proposed Community legislation.

Issues Discussed

There was considerable confusion among those most familiar with the EU regulatory environment for microorganisms about the objective of the entire QPS process. As I understand it, there is currently no Community-wide regulation of microorganisms used in the production of food for humans or as probiotic organisms, while microorganisms used in the production of animal feeds are tightly regulated at the individual country level. Many individuals asked—with a fair level of concern—whether the QPS initiative presaged a change in this regulatory environment. The EFSA representatives insisted that it did not, but I admit that the potential application of the system is not clear to me.

Putting aside this question, most attendees agreed that it is appropriate to develop a harmonized approach to the assessment of the safety of microorganisms. A number of contentious scientific issues emerged.

1. Where will the boundaries be drawn? Will it encompass “traditional fermentations” in which the culture(s) used is(are) ill-defined or spontaneously derived? I was surprised to learn that many large production facilities use cultures that are only partially defined or not defined at all.
2. Antibiotic resistance determinants, particularly in relation to those organisms commonly used in the preparation of human foods, was seen as an extremely difficult area, partly because of the limited available data regarding patterns of antibiotic resistance and lack of standardization, and partly because some level of antibiotic resistance is known or suspected to be common among bacterial strains in common use. It was argued that antibiotic resistance has not been recognized as a problem in foods and there is no evidence to suggest that this form of human exposure has led to any measurable increase in resistance to antibiotics of

clinical importance. Consequently the continuing use of existing strains should not be placed in jeopardy.

3. The need for an unequivocal identification of strains, and questions regarding the appropriate taxonomic level (genus, species, subspecies, strain) needed in order to make valid generic statements regarding safety. There was uncertainty whether identity should always reflect the state of the art or whether identity based on phenotypic criteria would be sufficient. There were some concerns that smaller companies may not have the facilities to undertake extensive taxonomic studies. In addition, it was pointed out that several microbial groups which might be eligible for QPS status are poorly understood and their taxonomy is undergoing almost continuous revision. There was extensive discussion of the potential impact of redefining a strain's taxonomic classification upon its QPS status.

Many participants argued that it should never be necessary to characterize bacterial strains beyond the species level. I disagree, and so did the Discussion Group 2 recommendation, which suggested the subspecies level for lactic acid bacteria and the species level for most yeasts.

4. The question of whether taxonomic units that include pathogenic strains are appropriate for inclusion in QPS. The consensus is that it should depend on the gene transfer potential—similar in some ways to issues regarding transference of antibiotic resistance; most individuals were reluctant to rule out the possibility of some *Staphylococcus* or *Enterococcus* strains, for example, being regarded as generally safe based on history of past use.

5. Finally, I feel strongly that any strain that is to be regarded as safe based on history of use must be deposited in a recognized culture collection, but this was far from universally agreed to. Many individuals argued on the basis of confidentiality or economics that such deposit should not be required.

Next Steps

As noted above, a new EFSA working group is considering the recommendations and conclusions of the colloquium and revising the working paper on QPS. It is expected that a final report on the QPS approach will be available by summer of 2005.