

Synthesis of ILSI Risk Assessment-Related Activities
Past Accomplishments and Future Directions
September, 2005

I. Background

Risk assessment issues (specifically as they related to the safety of food containing caffeine and artificial sweeteners such as saccharin) provided the key impetus for the creation of ILSI over 25 years ago. Risk assessment became institutionalized as an area of focus for ILSI following the challenge put forth by Dr. Frank Press, then President of the National Academy of Sciences, in September, 1983 (Press, 1984). The Academy's landmark publication entitled "Risk Management in the Federal Government: Managing the Process" had been issued a short time earlier (NRC, 1983). In his keynote address at the Symposium on Safety Assessment: The Interface between the Science, Law and Regulation, he presented his vision in which ILSI would, with support from its member companies, create "a mechanism for research on the scientific issues underlying risk assessments." He gave it a name (the Risk Science Institute) and proposed that it would do "first-class, long-term research to reduce the uncertainties of risk assessment." Less than two years later, the Risk Science Institute (RSI) was established , funding over 80 researchers at a total of \$5 million over a 10+ year period.. Additional funds also became available from both internal and external sources to do manage research in-house. This continues today, while the external research program, regrettably, does not.

The Risk Science Institute is not the only ILSI entity involved in risk assessment activities, however. While ILSI, as a whole, has matured into one that also addresses conundrums in other areas of science such as nutrition and biotechnology, activities related to risk assessment remain a prominent component of its portfolio in ILSI's branches around the world as well as the Research Foundation institutes. All have supported a wide variety of risk assessment-related activities, including scientific research, development of risk assessment tools and principles, and risk assessment training as well as dissemination of risk assessment-related information through publications, seminars, and workshops. ILSI brings a number of unique strengths to these efforts, including a reputation for scientific integrity, the global reach and perspective of the ILSI entities, and the ability to provide a neutral forum for discussions among scientists from academia, government, industry and the public interest/public health sectors. Moreover, ILSI has the flexibility to identify gaps in knowledge, focus on key issues, and often can move more quickly than many other organizations or government to develop research data, assessment tools/principles, and dissemination/training activities. This flexibility gives ILSI the opportunity to make a significant contribution to the development of the data that can be used in risk assessment and the development of the assessment tools, themselves.

A summarization of the 25+ years of ILSI's efforts related to risk assessment would yield a document of encyclopedic weight. This report focuses on a shorter time frame-with an emphasis on the past five years. Nonetheless, it will be apparent that ILSI has made, and continues to make, significant contributions to the field of risk assessment. The report

summarizes many, but not all, of the ILSI risk assessment-related activities and accomplishments within the five-year time frame, and offers suggestions as to possible directions for future efforts. Some of the information about past and current activities was supplied by some of the ILSI branches for inclusion in the Risk Assessment Matrix or in response to a special request. In that request, all of the ILSI entities were asked to provide 1-3 examples of activities they supported over the past five years that they believed have had, or were expected to have, the greatest impact. Examples of high impact activities were provided as a guide for making their determinations.

II. Past and Current ILSI Activities Related to Risk Assessment

ILSI activities relating to risk assessment have included support of scientific research "at the bench," research resulting in the development of risk assessment tools, and the dissemination of information and training. This section of the report will summarize these activities.

A. Scientific Research

For purpose of this report, ILSI activities in scientific research "at the bench" related to risk assessment are classified into two general categories: 1) "new" research developed by individual investigators or teams and 2) multi-laboratory collaborations for the purpose of evaluation of new or existing experimental systems.

"New" Research:

Allergens

For over a decade, through early 2004, the Allergy and Immunology Institute (AII) sponsored \$1.5 million of basic research to develop an infrastructure of technical and scientific expertise and improve scientific understanding of the immunologic, pathologic, and physiologic mechanisms of adverse reactions to foods. AII's funding was used to strengthen existing research programs, support promising investigators early in their careers, encourage food scientists to undertake food allergy research, and provide supplementary funds for young investigators to secure fellowships in the area of allergy and immunology. Investigators who benefited from this support early in their careers have become an invaluable source of information and expertise on adverse immunologic responses to foods for ILSI's industry members.

AII-funded research has:

- provided significant insight into the association between food allergy and airway disease and, for the first time, provided unequivocal evidence for the pathogenic role of food hypersensitivity in a subset of patients with asthma,
- characterized a major wheat allergen and confirmed its ability to sensitize patients by ingestion as well as inhalation,

- found considerable structural similarities between a specific soybean and peanut allergen-possibly supporting an emerging hypothesis that early exposure and sensitization to peanut allergens may increase the possibility of developing soy allergy,
- identified immunologic parameters associated with the development of oral tolerance in children with cow's milk allergy that can help clinicians predict which patients will ultimately lose their clinical reactivity to cow's milk and when future food challenges should be scheduled to reevaluate reactivity,
- identified an immune feature of peanut-allergic individuals that could lead to new therapeutic approaches to treat potentially fatal reactions,
- demonstrated cross-reactivity-an important component to consider in diagnosing food allergy and designing more specific tests-between banana and latex allergens as well as allergens in walnut and tree nut, pecan, cashew, hazelnut, and almond,
- cloned genes encoding two major walnut allergens that might one day be used to design a vaccination approach for the treatment of walnut food allergy, demonstrated a significant role of certain types of immune responses in producing airway hyper-responsiveness and inflammation in a mouse model-important research that can improve our ability to model and eventually modulate discrete functions of the immune system to restore balanced responses, and elucidated underlying immune mechanisms that induce the changes in gastrointestinal (GI) function seen in adverse reactions to foods that may one day help us find and treat the immunologic pathologies of the GI tract involved in food allergy.

Biotechnology

ILSI plays a critical role locally and globally in developing, communicating, and advancing the scientific underpinnings for the safety assessment of agricultural products including those developed by agricultural biotechnology. Through its global presence, ability, and charter to engage scientists across numerous disciplines and interests, ILSI serves as a key scientific resource for scientists and decision-makers around the world for information and expertise relating to the safety assessment and nutritional evaluation of foods and feeds derived from agricultural biotechnology products. ILSI branches and the ILSI International Food Biotechnology Committee have collaborated and established relationships with national and international scientific organizations and regulatory agencies. ILSI has been instrumental in developing and publishing recommendations for science-based safety assessments for a decade and a half, including:

- Collaborative publication with the International Food Biotechnology Committee in 1989 to establish the key scientific bases for assessing the safety of foods derived from products produced using agricultural biotechnology.

- Working with leading food allergy experts to develop and publish in 1996 the first decision-tree approach for assessing the allergenic concerns related to consuming foods derived from products produced using agricultural biotechnology.
- Developing and creating in 2002 a public database on the composition of grain from key agricultural crops that serves as a basis for comparing the composition of grain produced using agricultural biotechnology to conventionally-bred grain.
- Developing and publishing in 2003 with international academic experts guidance for the appropriate conduct and assessment of studies to compare the animal feed performance of grain derived from products produced using agricultural biotechnology to conventionally-bred grain.
- Collaborating with international scientific experts in 2004 to provide the scientific rationale and global consensus recommendations for conducting the nutritional and safety assessment of food derived from nutritionally-enhanced crops developed using agricultural biotechnology.

ILSI activities related to agricultural biotechnology have been consistently successful due to the quality of science, the quality and reputation of local and international presenters, the ability to identify and have key local experts attend and participate, and the ability of ILSI to provide appropriate follow up, including reports and publications. A list of specific outcomes of these activities, outlined in a separate document, helps realize the success and importance of ILSI's role in advancing the science in the area of agricultural biotechnology. Through these activities, ILSI built a reputation as an organization that develops and shares advanced scientific knowledge on food biotechnology through a great network of experts and collaborations with organizations (e.g., WHO, FAO, OECD) as well as government agencies concerned with plant biotechnology.

Chemicals

Acrylamide. The ILSI Europe Task Force (TF) in collaboration with ILSI NA and ILSI RSI published a review article focusing on exposure assessment and internal dose assessments of acrylamide in food, which contributed to the risk assessment of acrylamide in food and helped to understand the impact on public health. The article was provided to the FAO/WHO Joint Expert Committee on Food Additives (JECFA) for their evaluation of acrylamide in February 2005. ILSI North America's Technical Committee on Food Toxicology and Safety Assessment and its Scientific Advisor from the Risk Science Institute have been active in the development of the U.S. research strategy to address hazard and exposure issues related to the finding of acrylamide residues in certain foods.

*Fumonisin*s. ILSI North America's Technical Committee on Food Toxicology and Safety Assessment, at the request of the U.S. FDA, has provided partial funding for a study on fumonisin-induced cardiovascular and atherogenic disease. The goal of the study, using pigs as the model for human disease, is to improve risk assessment of fumonisins by developing dose-response data for the cardiovascular endpoint. This Committee also funded a USDA research project comparing the effects of corn processing techniques on the content of fumonisins.

Evaluation of new or existing experimental systems

In October 2001, the ILSI HESI Technical Committee on Alternatives to Carcinogenicity Testing published the results of its collaborative research program on "Evaluation of Alternative Methods for Carcinogenicity Testing." The program consisted of the generation of data on 21 chemicals in six alternative whole animal systems. Over 50 laboratories worldwide participated in the data collection. The outcome of this effort has allowed for improved understanding of the strengths and limitations of each of the six models.

'Omics technology (i.e., genomics, proteomics, metabonomics, etc.) holds the promise of improving our capacity to better understand the mechanisms and metabolic pathways of toxicity. To that end, ILSI HESI established a committee on Application of Genomics to Mechanism-based Risk Assessment. The objectives of the Committee include comparative evaluation of existing and evolving experimental methodologies for measuring alterations in gene expression so as to understand their sources of variability, their sensitivities, and the challenges in sharing and comparing data from a variety of experimental systems applied in a number of laboratories worldwide. As data accrue, they, along with data generated in other settings, will be evaluated for their ability to determine if known pathways of toxicity can be associated with characteristic gene expression profiles.

Pathogens

North America's Technical Committee on Food Microbiology has provided funding for research projects directed to expanding the knowledge base on foodborne pathogens. Topics include *Listeria monocytogenes* virulence and pathogenicity; antibiotic resistance and the risk to human health of farming practices; on-farm ecology and factors influencing bovine colonization of *E. coli* 0157:H7; and, development of model systems to filter microbial pathogens from animal agricultural run-off water.

B. Development of Risk Assessment Tools and Principles

Activities related to the development of risk assessment tools and principles constitute a large portion of resource commitment for several of the ILSI entities, e.g., the Risk Science Institute, ILSI Europe, ILSI HESI and ILSI NA.

Risk assessment is defined in the draft FAO/WHO/ICD/ILSI Risk Analysis Manual and elsewhere as "a scientifically based process consisting of the following steps: i) hazard identification; ii) hazard characterisation; iii) exposure assessment; and iv) risk characterisation." Each of ILSI's efforts in the area of risk assessment has covered at least one and sometimes more of the four phases of risk assessment.

Chemical-specific projects:

Occasionally, ILSI's attention is focused on specific chemicals. In recent years, white papers have been developed on the toxicity of the mycotoxin, deoxynivalenol, and on the toxicity and metabolism of acrylamide (ILSI NA). ILSI NA worked with FDA's National Center for Toxicological Research in developing a physiologically-based pharmacokinetic (PBPK) model for acrylamide metabolism in rodents and humans. The output of this effort is being provided to the FAO/WHO Joint Committee of Food Additives and Contaminants for use during its upcoming evaluation of acrylamide as a food contaminant. ILSI Europe has initiated a series of publications on chemical substances present in food packaging materials (e.g., Polyethylene terephthalate, Polystyrene, Polypropylene, Polyethylene, PVC) and is convening an Expert Group charged with developing guidelines on exposure assessment for food packing materials.

Pathogen-specific projects:

ILSI's attention also is focused on specific foodborne pathogens. In the past two years, both ILSI Europe and ILSI RSI/ILSI NA have drafted reports which address specific examples. ILSI Europe has issued publications on transmissible spongiform encephalopathies (including BSE) and the food chain, on the parasites *Cryptosporidium*, *Cyclospora* and *Giardia*, and on foodborne viruses. The ILSI/ILSI NA collaboration on updating the science base for *Listeria monocytogenes* risk assessment has been completed, and it has been proposed that the same be done for *Escherichia coli* 0157:H7.

Children as a potentially sensitive population:

Increasingly, attention is being given to the challenge of understanding if, how and when children may respond differently from adults to exposures to chemicals, be they environmental, pharmaceutical or in other categories. Some of this attention is prompted by legislative mandates or regulations (e.g., the 1996 Food Quality Protection Act (FQPA) and Safe Drinking Water Act (SDWA) amendments or U.S. FDA's Pediatric Rule in the U.S.); some is prompted by the accumulation of data worldwide reflecting specific examples of differential sensitivities. In the past year, the WHO/ILO/UNEP International Program on Chemical Safety (IPCS) began a global assessment of children's environmental health, modeled on its recently-completed *Global Assessment of the State-of-the-Science of Endocrine Disruptors*.

Over the past 15 years, the ILSI Risk Science Institute has developed a body of work related to children's health issues, with an emphasis on the consequence of exposures to pesticides. However, it should be noted that risk assessment tools and principles developed to address issues related to pesticides are generally applicable to chemicals of all kinds, and, in many respects, also to food-and water-borne pathogens. The 1992 publication of *Similarities and Differences Between Children and Adults* predated the National Academy of Sciences' pivotal work on *Pesticides in the Diets of Infant and Children* by a year and had a significant impact on the topics addressed and the nature of the recommendations made in the NAS study. In turn, many of the recommendations made in the NAS study were translated into legislative language in FQPA and SDWA. The child-specific and other new provisions included in FQPA and SDWA led to the development of over 20 science policy guidance documents by the U.S. EPA. Most of these documents were based upon relevant science-based projects and publications developed by ILSI RSI.

Following completion of this first round of FQPA-related work, ILSI RSI took on the task of developing a risk assessment framework specifically for children. Based, in part, upon the generic risk assessment framework that U.S. EPA had previously developed, the draft *Framework for Assessing Risk to Children from Environmental Agents* prompts the risk assessor to address all of the scientific elements of the risk assessment from a child-centric point of view so that s/he will fully describe the potential for harm (or, lack thereof) of specific exposure scenarios and better communicate the findings to the decision-maker and other stakeholders. The draft Framework is serving as the principal resource for the U.S. EPA in its effort to develop its own children's risk assessment framework and it also is expected to be used by IPCS as it proceeds with its initiative on children's environmental health.

The Pediatric Rule of the U.S. Food and Drug Administration speaks to the expectations of the Agency if and when pharmaceutical companies decide to develop and seek approval of a new drug or new uses of existing drugs specifically for children. ILSI HESI's Developmental and Reproductive Toxicology Technical Committee has been sponsoring a project for several years (i.e., the Juvenile Animal Studies in Assessment of Pediatric Safety project) which seeks to determine when juvenile animal studies are needed in safety assessment and to address the design of such studies. A series of papers describing the characteristics of eight organ systems in humans and relevant test species have been published. Additional papers are planned.

Database development:

The quality of risk assessments is highly dependent upon the quantity and quality of the hazard and exposure data available for the assessment. To that end, many organizations including ILSI entities, have created repositories of agent-specific or species-specific information, some of which is publically-available, some of which is proprietary.

- ILSI HESI's Structure Activity Relationship Database Technical Committee has supported the development of an international database of chemical-specific toxicity testing results, including biological toxicity data, physicochemical data and molecular structure information for predictive toxicology. The pilot database contains information on five endpoints: carcinogenicity, mutagenicity, dermal sensitization, hepatic toxicity and safety pharmacology. By the end of 2003, the database contained more than 2700 structures and data on more than 4500 chemicals.
- ILSI HESI's Technical Committee on Risk Assessment Methodologies has made publically-available its Residential Exposure Factors Database. The database houses non-chemical-specific information which can be used to support probabilistic residential exposure assessment.
- ILSI HESI's Technical Committee on Toxicogenomics is developing a database in collaboration with the European Bioinformatics Institute which will house the microarray data generated in its collaborative research program. The information in this database will be publically-available.
- ILSI RSI recently completed assembling a publically-available database which contains non-chemical-specific physiological parameters for humans and rodent species commonly used to develop chemical-specific test data for use in risk assessment. Data on physiological parameters are of particular value when extrapolating from animal data in human health risk assessments.
- ILSI Southeast Asia Region has been nominated by the ten ASEAN countries to develop and host the ASEAN Food Safety Standard Database for on-line access. The database is an outcome of the Food Safety Standards Harmonization Workshop series organized by ILSI SEA Region in collaboration with ASEAN food safety regulatory bodies, and with support from the ILSI/ FAO framework. The database will serve as an ongoing monitor of the progress of ASEAN Food Safety Standards Harmonization initiative. The regional database was launched during the 4th ASEAN Workshop in November 2004.
- The International Organizations Committee has provided support for developing approaches to collect country- and region-specific food consumption information via the ILSI RSI Advisory Committee on Microbial Risk Assessment (MRA). These "local" data sets would provide officials with the ability to refine a global assessment of a pathogen or food chemical/contaminant or nutrient to fit the local situation and to prepare additional assessments on representative of these categories of food constituents that are of local, but not necessarily global, interest. Other key data needs identified by the MRA Advisory Committee are in the areas of burden of foodborne/waterborne disease and incidences and levels of microbial contamination of foods. Capacity-building in developing countries will be a relevant factor in the success of such data collection.

- ILSI Europe's Food Chemical Intake Task Force is exploring the value of the supermarket fidelity card as a source of data for refined food intake assessment. Currently there are no pan-European food consumption data, and the existing national databases cannot be compared to solve this problem. Probabilistic models like Monte Carlo are well established, but the quality of the outcome of such a method still depends on the quality of data input, i.e. estimates of food consumption. The Task Force has started collaboration with a Swiss retailer. The aim is to explore what data could be made available from their fidelity cards. Important questions are: How sound are the data? What proportion of a household's food consumption is provided by retailers? How does confidentiality limit this approach?

After having checked if the retailer's households are comparable with the Swiss Federal Office of Statistics data on household composition, the Task Force has selected an easy-to-quantify colourant, sunset yellow E110. They looked into the number of products containing this colourant, and the number of households that buy at least one of these products. A telephone survey has been organised to get further information on the households' compositions so that exposure to the colourant can be quantified. This method is of course not "the" answer for intake assessment but can be part of it, as a complementary tool to other surveys currently used. This method has the advantage to provide the actual composition of foods and actual quantities of products purchased at the retailer. The results of this case study are now being analysed and will be published early 2006.

Since the European Food Safety Authority (EFSA) and other groups in Europe are also working on exposure assessment, the Task Force will inform the EFSA's Scientific Committee and EFSA's Additives and Food Contaminants Panel on the outcome of this collaborative work. Depending on the quality of the results, a workshop focussing on the harmonization of methods for exposure assessment, and on the feasibility and opportunities to further develop retailers' databases in collaboration with the key stakeholders will be considered.

Testing Strategies for Chemical Risk Assessment:

It is common to rely upon data developed in laboratory animal studies when conducting human health risk assessments. In some cases, such as for pesticides and pharmaceuticals, testing requirements are imposed as a prerequisite to approval to market the product. In other cases, e.g., commodity chemicals, less robust pre-market requirements exist. For many agents, governments develop the desired toxicity data.

Four recently-completed ILSI-sponsored projects promise to contribute to the updating and improvement of toxicity testing strategies for chemicals and other agents.

- ILSI RSI's project on fibers developed an approach for considering how available *in vitro* and shorter-term *in vivo* methods might be combined in a testing strategy to assess the likelihood that particular manmade fibers may present a hazard and

therefore may be candidates for further (e.g., long-term) testing by the inhalation route.

- ILSI RF/RSI's project on development of a screening strategy for the hazard identification of engineered nanomaterials. The three key elements of the toxicity screening strategy are: Physicochemical Characteristics, *In Vitro* Assays (cellular and non-cellular), and *In Vivo* Assays. Oral, dermal, inhalation, and injection routes of exposure are included recognizing that, depending on use patterns, exposure to nanomaterials may occur by any of these routes. Tier 1 *in vivo* assays are proposed for pulmonary, oral, skin and injection exposures, and Tier 2 evaluations for pulmonary exposures also are proposed. Tier 1 evaluations include markers of inflammation, oxidant stress, and cell proliferation in portal-of-entry and selected remote organs and tissues. Tier 2 evaluations for pulmonary exposures could include deposition, translocation, and toxicokinetics and biopersistence studies; effects of multiple exposures; potential effects on the reproductive tract, placenta, and fetus; alternative animal models; and mechanistic studies. A manuscript is being submitted for publication in *Particle and Fibre Toxicology*.
- ILSI RSI's project on the development of a *Framework for Use of Screening Tools for Potentially Toxic Chemicals in Context-based Decision-making* provides a mechanism for determining "How Much Data is Enough?" when needing to make specific risk-based decisions.
- ILSI HESI's Agricultural Chemical Safety Assessment project led to the development of an improved toxicity testing scheme for agricultural chemicals.

Development of Test Guidelines:

Allergens

All's Scientific Advisors developed guidelines for the conduct of double-blind, placebo-controlled food challenges to test for food allergies in humans. These are now being used in the U.S. and elsewhere.

Chemicals

The quality of data generated in human or laboratory animal studies is highly dependent upon the integrity of the process by which they are developed. In the regulatory setting, greater comfort with the quality of the results often exists when the data have been generated according to formal, standardized test guidelines or protocols. ILSI entities have been, and continue to be, involved in the development and/or standardization/validation of, and/or assessment of results from, specific testing protocols.

- ILSI RSI supported a project which led to the identification of desirable characteristics of a protocol which would evaluate neurotoxicity in the developing

organism. This work was used by U.S. EPA to craft its test guidelines for developmental neurotoxicity. Currently, ILSI RSI is sponsoring a project which is evaluating data for a number of chemicals generated according to the guideline to determine if it is working as expected.

- Over the course of development of the developmental neurotoxicity test guideline, the question was raised as to whether or not the newborn test animals were being directly exposed to the agent of interest. There are human exposure scenarios in which this is known or expected to be the case. The ILSI RSI manual on *Direct Dosing of Pre-weaning Mammals in Toxicity Testing and Research* offers factors to consider and guidance when it is deemed desirable to study this particular exposure paradigm.
- ILSI HESI's Immunotoxicity Technical Committee has proposed a test protocol for evaluating the potential for effects on the immune system of the developing organism.

Risk Assessment Frameworks:

Chemicals

Risk assessment framework for chemicals in foods. It was noted earlier that ILSI has been involved in the development of a risk assessment framework for children. The organization also has been involved in the development of more generic risk assessment tools and principles. One project of particular import was ILSI Europe's project 'Food Safety in Europe (FOSIE): Risk Assessment of Chemicals in Food and Diet,' a three year European Commission Concerted Action funded via the EC Fifth Framework Programme (2000-2003). A collaborative, multidisciplinary, and primarily European network was established to critically assess the current knowledge in risk assessment and to examine the science base for new qualitative and quantitative methodologies for risk assessment for various food chemical categories. The aims of the project were:

- To explore means of improving the principles applied to, and scientific basis of, risk assessment with respect to food additives and contaminants, micronutrients and nutritional supplements, macronutrients and whole foods.
- To consider possible interactions between individual chemicals and effects of the food matrix.
- To identify the gaps in knowledge that might lead to differences in interpretation of toxicological and exposure data, and the research needs to reduce these.
- To determine the nature and level of testing needed for safety evaluation relevant to the nature of the chemical, level of use/occurrence in the diet and human exposure.

- To add a European contribution to international initiatives to harmonise principles, terminology and methodology for risk assessment.
- To contribute towards a consensus on risk assessment issues that is scientifically transparent and justifiable.
- To assist risk managers in developing appropriate, defensible food standards that adequately protect the safety of the consumer while allowing for innovation in food production and processing.

Six Individual Theme Groups (ITGs) were organised to consider the first three steps of the risk assessment process as follows:

- Hazard identification by methods of animal-based toxicology
- Methods of *in vitro* toxicology
- Hazard characterisation of chemicals in food and diet: dose-response, mechanisms and extrapolation issues
- Mathematical modeling and quantitative methods
- Assessment of intake from the diet
- The contribution of epidemiology

The reports from these six groups, covering current status, limitations, reliability, potential for improvement and gap analysis and research needs, were published in *Food and Chemical Toxicology* (Volume 40, No 2/3, pages 137-427). Based on the outcome of the original ITG papers, a final ITG on Risk Characterisation prepared one integrated document on the characterisation and quantification of risk in the food area. Their paper on the characterisation and quantification of risk in the food area, has been published in *Food and Chemical Toxicology* (2003, volume 41, pages 1213-1271). The paper provides the reader with risk characterisation schemes for the following different classes of food chemicals: chemicals of low molecular weight, micronutrients and nutritional supplements, macronutrients and whole foods. The paper concludes that risk characterisation is an iterative process of which the outcome depends on the question to be addressed, the nature of the substance, the available data and the nature of the hazard. In addition to the paper, the final project results have been published separately in a triptych newsflash.

ILSI Europe is now following up on the outcome of the FOSIE project and just submitted a three-year project on risk-benefit analysis for foods (BRAFO) under the 6th Framework Programme of the European Commission. The objective is to propose a science-based framework to quantify the benefits and risks in foods and food compounds.

Human Relevance Framework (HRF) for analysis of mode of action data and information. Understanding how chemicals exert their effects, i.e., their mode of action (MOA), is critical to understanding the importance of exposure to such agents in the human. In November, 2003, ILSI RSI published a study using animal and human MOA information to generate a four-part Human Relevance Framework (HRF) for systematic and transparent *relevance* analysis of MOA data and information. Based mainly on case studies of non-DNA reactive carcinogens, the HRF features a “concordance” analysis of “key events” in the MOA based on information from both animal and human sources, with a focus on determining the appropriate role for each MOA data set in human health risk assessment. The ILSI RSI Human Relevance Framework has been incorporated into the 2005 final version of U.S. EPA's cancer risk assessment guidelines and also is being used as the basis for the updating of the 2001 IPCS Cancer Mode of Action Framework.

The risk assessment community is moving away from the use of long-standing default principles and practices that rely on sharp distinctions between analyses for carcinogenic effects and those for health effects other than cancer. Some such distinctions are science-based, but most originated as policies to address scientific uncertainties. A new ILSI RSI report, to be published as a series of three papers in October, 2005, demonstrates the further applicability of the HRF for reproductive, developmental, neurologic, and renal endpoints, to ongoing efforts to harmonize risk assessment principles and practices. The specific cases illustrate the critical importance of developmental or life stage in reaching conclusions about the comparability of MOA information from animal and human sources. Based on qualitative and quantitative MOA considerations, MOA/human relevance analysis also contributes to identifying research data needs and issues essential for the dose-response and exposure assessment components of the overall risk assessment.

Threshold of toxicological concern for chemical substances present in the diet. The threshold of toxicological concern (TTC) is a pragmatic risk assessment tool that is based on the principle of establishing a human exposure threshold value for all chemicals, below which there is a very low probability of an appreciable risk to human health. The concept that there are levels of exposure that do not cause adverse effects is inherent in setting acceptable daily intakes (ADIs) for chemicals with known toxicological profiles. The TTC principle extends this concept by proposing that a de minimis value can be identified for many chemicals, in the absence of a full toxicity data base, based on their chemical structures and the known toxicity of chemicals which share similar structural characteristics. The establishment and application of widely accepted TTC values would benefit consumers, industry and regulators. By avoiding unnecessary toxicity testing and safety evaluations when human intakes are below such a threshold, application of the TTC approach would focus limited resources of time, cost, animal use and expertise on the testing and evaluation of substances with the greatest potential to pose risks to human health and thereby contribute to a reduction in the use of animals.

An Expert group of ILSI Europe has examined the TTC principle for its wider applicability in food safety evaluation. The Expert Group examined metabolism and accumulation, structural alerts, endocrine disrupting chemicals and specific endpoints, such as neurotoxicity, teratogenicity, developmental toxicity, allergenicity and immunotoxicity and determined whether such properties or endpoints had to be taken into consideration specifically in a step-wise approach. The expert group concluded that the TTC principle can be applied for low concentrations in food of chemicals that lack toxicity data, provided that there is a sound intake estimate (Food and Chem. Tox. Vol. 38, n°2-3, pp.255-312, 2000 and Vol. 39, n°9, 893-905, 2001). The use of a decision tree to apply the TTC principle was then proposed, and another paper describes the step-wise process in detail (Food and Chem. Tox. Vol. 42, n°1, pp.65-83, 2004). The initial step of the decision tree is the identification and evaluation of possible genotoxic and/or high potency carcinogens. Following this step, non-genotoxic substances are evaluated in a sequence of steps related to the concerns that would be associated with increasing intakes. For organophosphates a TTC of 18 μ g per person per day (0.3 μ g/kg bw/day) is proposed, and when the compound is not an OP, the TTC values for the Cramer structural classes III, II and I, with their respective TTC levels (e.g. 1800, 540 and 90 μ g per person per day; or 30, 9 and 1.5 μ g/kg bw /day), would be applied sequentially.

In order to make the TTC concept known to a wider audience, the task force published a Concise Monograph with the title “Threshold of Toxicological Concern (TTC) – A tool for assessing substances of unknown toxicity present at low levels in the diet” in 2005. The booklet aims at explaining the history and development of the principle and its application to chemicals present at low levels in food to the scientific lay-reader.

After having developed and disseminated the science of the Threshold of Toxicological Concern concept, the task force will now evaluate the applicability of the concept to trace substances in food.

Risk assessment of genotoxic carcinogens in food. Improved analytical methods are capable of detecting very low concentrations of chemicals. This has revealed that foods can contain low levels of genotoxic carcinogens, including man-made chemicals such as ethyl carbamate, nitrosamines or heterocyclic amines, and also natural chemicals like methyl eugenol in basil. Carcinogens are chemicals that can increase the occurrence of tumors. The carcinogens that can damage DNA are referred to as genotoxic. There is no international consensus on how to evaluate the risk of genotoxic carcinogens in food. In Europe, the former Scientific Committee on Food (SCF; now European Food Safety Authority) has advised on the assessment of genotoxic carcinogens in the diet on a case-by-case basis using a graded "weight of evidence." In the USA, however, a quantitative hazard characterisation is performed by mathematical low-dose extrapolation of animal data, using a linear model as the default. There are more and more data on cell repair mechanisms, like DNA repair. This would imply a non-linear relationship between lower doses and development of cancer; some data even suggest that a low exposure to carcinogens may actually reduce the incidence of tumours.

The ILSI Europe Risk Assessment of Genotoxic Carcinogens Task Force (TF) aims to review how to quantitatively assess cancer risk from low dietary exposure to genotoxic carcinogens. The results may contribute to the prevention of diet-related cancer. An Expert Group (EG) developed a risk assessment framework for genotoxic carcinogens in food. The experts reviewed available data on low-dose effects of selected genotoxic compounds. Evidence ranging from DNA binding studies to mechanistic investigations using both in vitro and in vivo data has been explored to investigate the assumption of linearity of dose-response relationships. In vitro models for hazard identification and characterisation have been reviewed for appropriateness, including the presence and activity of relevant mechanisms (e.g. activation, cytoprotection, DNA damage, DNA repair). The group also evaluated difficulties associated with the use of standard animal bioassays for carcinogen characterisation.

Based on the above information, the EG critically evaluated risk assessment principles of low dose genotoxic carcinogens and recommended how to advance them. The scientific evaluation of the available data is of key importance because of its major impact on regulatory and risk management strategies. In addition, more transparent and harmonised risk assessment procedures may improve consumer confidence in regulatory processes.

The Expert Group on Genotoxic Carcinogens has a close working relationship with the European Food Safety Authority (EFSA) and the World Health Organization – International Programme on Chemical Safety (WHO/IPCS), and shares the development of the framework document with them. EFSA developed guidelines for a harmonised risk assessment of genotoxic carcinogens. IPCS organised a workshop to develop “Environmental Health Criteria on Principles of Modelling Dose-response of Risk Assessment of Chemicals.”

EFSA and WHO will, in collaboration with ILSI Europe, host an international conference in November 2005 under the title “Risk assessment of compounds that are both genotoxic and carcinogenic –New approaches” to identify the main conclusions, recommendations,

and future research needs. Based on the working papers developed by the organisers and considering any additional perspective seen as relevant, the conference will discuss

- the possibilities of risk assessment advice for genotoxic and carcinogenic compounds with focus on low intakes as expected from foods;
- the interpretation of the outcome of the approaches in terms of risk to human health ;
- how well new risk assessment tools meet the needs of risk managers and can provide the possibility for practical options in situations where elimination of such risks is not to be expected.

These discussions will help to identify knowledge and research gaps and may lead to proposals for improvements. The outcome of this joint conference will be published in a peer-reviewed journal.

Risk Assessment Model Software

In late 2003, the ILSI Research Foundation acquired the risk assessment model CARES[®] (the Cumulative and Aggregate Evaluation System) from CropLifeAmerica, its original sponsor. This state-of-the-art software tool was designed to conduct complex aggregate and cumulative pesticide risk assessments in response to elements in the 1996 Food Quality Protection Act which updated the pesticide regulatory mandates in the U.S. The model is able to integrate data on pesticide residues in specific foods and on non-food surfaces such as lawns or carpets along with food and drinking water consumption with representative toxicity values to estimate the risk from each single source-food, drinking water and residential-or, the combination of two or all three sources. This can be done for a single chemical (aggregate risk assessment) or for a group of substances (cumulative risk assessment). This model holds great promise for expansion. The substance being evaluated need not be a pesticide. Data on food components including nutrients, food contaminants other than pesticides or pathogens could be substituted for those on pesticides, and similar aggregate and/or cumulative analyses conducted.

C. Dissemination of Risk Assessment-Related Information/Risk Assessment Training

A substantial number of the activities relating to risk assessment identified by ILSI entities have been directed towards the dissemination of information. ILSI entities have supported the publication of many reports, including proceedings of workshops, technical and scientific reviews, and journal articles. A wide array of meetings and workshops also have been conducted to discuss and build consensus on risk assessment-related issues. In addition, many Branches have sponsored risk assessment training sessions, specific to food safety, pesticides, biotechnology, food allergens, microbial contaminants and/or general risk assessment principles. Much of this training is carried out via the FAO/ILSI Cooperative Framework of ILSI's International Organizations Committee which supplies training and capacity building for regulators in developing countries. A listing of some of the recent publications and workshops supported by the ILSI entities is provided in Appendix 3. A listing of some of the recent risk assessment training workshops

supported by the ILSI entities is provided in Appendix 3. Several examples which have had particularly significant impact are described below.

ILSI has long distinguished itself by the wide range and quality of its scientific publications and by its support of numerous technical meetings and workshops. As indicated by the extensive listings in Appendix 3, ILSI entities have been highly active and productive, both in producing publications and in their support of and participation in meetings and workshops.

The impact of these dissemination/training activities is hard to measure in quantitative terms. However, it is clear that ILSI has made a substantial contribution to the knowledge base relating to risk assessment and has brought together scores of scientists, health professionals, educators, and government officials for discussion of issues who otherwise would likely not have had such an opportunity. Some good high impact examples include:

1) The training workshops conducted as part of the FAO/ILSI Framework.

A workshop on Microbiological Risk Assessment was convened in May 2002 in Beijing. This workshop was immediately followed by a 2-week training course for 20 participants on MRA. Following these workshops, China started the nationwide microbial foodborne illness monitoring program, which is now a routine monitoring program of the Ministry of Health and implemented by the China CDC. This was just the beginning of active surveillance of microbial foodborne illness in China, but the ILSI workshop provided important scientific information and manpower training. Additional workshops on microbial risk assessment have been sponsored by ILSI Brasil and ILSI SEAR, all of which have improved the knowledge base of the regulators, the regulated industries academics and the medical and public health community.

A training manual on Risk Analysis has been developed by FAO in collaboration with WHO, ICD and ILSI (under the Framework). Training workshops, using the manual and its case studies as the principal teaching tools, have been presented in several settings under ILSI sponsorship, e.g., at a 2002 training workshop for Mercosur countries sponsored by ILSI Argentina, in conjunction with the 4th Asia Conference on Food and Nutrition Safety in March 2004 and in three presentations of ILSI RSI's Risk Awareness course to ILSI NA members and others in 2003 and 2004. In, 2004, ILSI South Africa provided training for people from several developing countries in Africa on the appropriate use of risk analysis in food regulatory decision making. So far, several hundred people have benefited from this training to date and it is anticipated that similar offerings will be repeated, since there is generally a high rate of turnover of food safety and other decision-makers, both within and outside of government.

2) ILSI India's October 2003 workshop on Risk Assessment of Pesticide Residues in Water and Food.

This workshop was organized on very short notice in response to increasing concern in the country about pesticide residues in water and water-based products and foods, identified in the absence of adequate government oversight and/or standards. Attended by over 200 delegates representing all concerned Ministries, research institutions, and industry, the symposium led to the following:

- Generation of data on presence of pesticide residues in raw agricultural products, water, milk, milk products, fish, poultry, soil, and human tissues
- Identification of causes for the presence of pesticide residues and remedial measures.
- Recommendations on steps to be taken to check the problem.
- Information on risk assessment of pesticide residues and how international safety norms are evolved.
- Emphasis on adoption of scientific approach to risk assessment for setting standards.
- Objective assessment of the situation and valuable inputs to the policy makers.
- Action points for government, industry, research institutions, agriculture and others.
- Acknowledgement of the importance of evolving food standards based on scientific criteria and in keeping with international norms, setting up world class adequate number of food analysis laboratories, code of conduct for NGOs and validation of results of analysis and transparency in a report by Joint Parliamentary Committee set up by Indian Parliament to investigate the matter. These recommendations are in line with recommendations made at the symposium.

The symposium was quite timely and demonstrated ILSI's ability to quickly respond to a problem area and get well-known technical experts and the key regulatory authorities as resource persons. The stories about pesticide residues in the media were adversely affecting the interests of industry and lack of credible response further aggravated the problems and created great deal of confusion in general public as well as government. The ILSI-India symposium was able to put facts before the stakeholders and brought into focus international norms and standards adopted in other countries.

3) The ILSI NA December 2001 bioterrorism workshop. The workshop was organized by The Food Microbiology and Food Toxicity and Safety Assessment Committees in

partnership with IAFP, CDC, FDA, NIH and USDA. The goal of the workshop was to discuss concerns about the potential for intentional microbial and chemical contamination of the food supply and to address the specific needs of ILSI NA members and associates, the major North American food companies, professional scientific organizations and government in ensuring food safety. It had high impact in that it was attended by key regulatory and industry representatives and it provided a synopsis of information on food bioterrorism that was not previously available.

4) ILSI NA-sponsored symposia at the annual meeting of the International Association of Food Protection. 2004 was the 12th year of this collaboration. These are of high impact in that they have often addressed (and brought to the forefront) new issues in food safety using highly qualified speakers that could provide cutting edge information. The topics for the last three years include antibiotic resistance, chronic wasting disease, *Listeria* research and foodborne listeriosis, shelf life dating, detection methods, evolution of foodborne pathogens and the "immunocompromised symposium" in 2004.

5) The annual ASEAN Food Safety Standards Harmonization Workshop

Recognizing the importance of harmonized food safety standards in the region to respond to the increasing global marketplace, the ILSI Southeast Asia Region Food Safety and Risk Assessment Task Force has taken the initiative to provide a platform for food safety regulators and decision makers of the ten ASEAN countries to discuss and evaluate their respective national food safety standards for potential consensus and harmonization within the region and with international Codex standards. It is also recognized that the lack of data on food consumption hinders the ability to generate country or region specific risk and exposure assessment. The workshops help identify gaps and enable the sharing of research data and information.

First held in 2001, the Workshop provides the scientific underpinnings and regulatory updates on selective food safety topics and international food safety standards development. The workshops led to consensus and concrete progress towards achieving food safety standards harmonization among the ASEAN countries with that of international standards. To-date, topics covered included additives such as intense sweeteners, colors, preservatives and flavoring compounds, as well as the setting of MRLs on contaminants, starting with selected mycotoxins and pesticides residues. ILSI plays a pivotal role in the facilitation and guidance of this scientific capacity building effort.

III. Impact of ILSI Activities in Risk Assessment Research, Tool Development, and Dissemination/Training

As has been noted, most of the ILSI entities have been actively engaged in risk assessment-related efforts for some time, and have made significant contributions in research, development of assessment tools and practices, and dissemination/training. The impact of these efforts may be somewhat difficult to measure, but it seems fair to say that ILSI is recognized by many government health officials and leading scientists

around the world as a consistent and credible contributor to the development of a relevant knowledge base and as a strong and engaged supporter of efforts to synthesize and disseminate information on risk assessment-related issues.

ILSI is unique in that it is one of only a very few organizations that can provide a neutral setting for fruitful discussions of key scientific issues by technical experts from industry, government, academia and the public interest/public health communities and the development of meaningful consensus positions on those issues. This reality notwithstanding, one must be mindful that "timing is everything." While it would be wonderful to boast that all of the projects, workshops, publications and research that ILSI has developed or sponsored over the years have been used to promote and assure wise decision-making by our stakeholders, the reality is that, sometimes, these outputs have not been used, either at the time they have been completed or later. Good science takes time and, sometimes, priorities change abruptly. We are all aware of the hot-issue-of-the-week mentality that often reigns in organizations. But, truth to be said, ILSI has had a very high rate of success in providing of information considered to be of high value.

Some specific examples of risk assessment activities that ILSI entities have been involved in over the past five years have been presented in Section II. The known or anticipated impact of some of these is described below.

A. Research Contributions

Allergens

Allergic reactions to foods can be minimal or fatal, depending upon the nature of the stimulus and response. Identification of sensitive individuals should not occur in a crisis mode. It is, thus, important to have reliable tools to identify those who may be sensitive before an episode occurs, to treat an episode successfully, should one occur, and if possible, to prevent episodes from ever occurring. The AII monies which supported research on food allergens added to the body of scientific knowledge in all of these areas. As importantly, some of the funding supported investigators who were early in their careers, helping them to get a foothold in their areas of interest and expanding the pool of expertise in issues surrounding adverse immunologic responses to foods.

Chemicals

ILSI NA's support of the toxicological studies on fumonisin has yielded data which assists in refining our understanding of the toxicological profile of this mycotoxin, especially the dose-response relationships and improving the quality and accuracy of this aspect of the risk assessment. Support for research on corn processing techniques leads to the development of ways in which fumonisin residues will be lowered in products, as consumed, and, thus, leading to a reduction in potential risk to human health.

HESI's collaborative program on alternative models for carcinogenicity testing as resulted in a major improvement in our understanding of the characteristics of each animal model, and its value in predicting the carcinogenic potential of test agents. As a result of this work, FDA's Center for Drug Evaluation and Research, and comparable authorities elsewhere in the world, have modified their pre-clinical study requirements for carcinogenicity to state, that for certain classes of drugs, testing in an alternative animal model may be substituted for testing by the conventional protocol in a second species (mouse). This constitutes a resource saving-in time, money and human resources, but is expected to provide the same level of information as would the traditional two-species, two-sex, lifetime studies.

B. Development of risk assessment tools and practices

As noted elsewhere, the Food Quality Protection Act of 1996 updates the pesticide regulatory mandates in the U.S. Included in that law were many proscriptive elements, describing what, and in some cases, how risk assessments were to be conducted. Special provisions were made for assessing risk to children (e.g., the 10X "extra" safety factor). Also, for the first time, EPA was obligated to make regulatory decisions on single commodity MRLs (maximum residue levels/limits) by estimating the total risk from that use as well as other existing uses and other non-occupational sources of exposure to that pesticide (aggregate risk assessment). In addition, in cases where the pesticide under evaluation shared a common mechanism of toxicity with other substance, the single use decision was to be informed by a cumulative risk assessment (combining of all non-occupational sources of exposure to the pesticide of interest with all non-occupational sources of the other substances). Many new science policies and risk assessment practices needed to be developed to successfully comply with the law. ILSI RSI and ILSI HESI supported many projects which developed many products (over a dozen by RSI, two by HESI) which became the foundation of the new EPA FQPA implementation guidance. In the nine years since FQPA was passed, EPA has made nearly 10,000 single MRL decisions, conducted hundreds of aggregate risk assessments and a small number of cumulative risk assessments. Regulatory and registrant decisions have led to many existing uses being removed, many new ones approved or denied, and many chemical registrations abandoned and new ones approved. These decisions were all based upon the Agency's new risk assessment practices, informed by the scientific information contained in the ILSI project outputs.

ILSI Europe's recently completed project 'Food Safety in Europe (FOSIE): Risk Assessment of Chemicals in Food and Diet,' a three year European Commission Concerted Action funded via the EC Fifth Framework Programme (2000-2003) is already having enormous impact, both within the EU and globally. The results contributed to European harmonisation (via the European Food Safety Authority) and international harmonisation of WTO. Refined risk assessment procedures of low molecular weight compounds, macronutrients, micronutrients & nutritional supplements and whole foods will result from this exercise. The outputs are being used as the principal basis for the Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food. These principles are used by the FAO/WHO Joint Expert Committee on Food Additives and the FAO/WHO Joint Meeting on Pesticide Residues in their hazard assessment activities leading to the development of Acceptable Daily Intakes and proposed CODEX MRLs.

The ILSI RSI Human Relevance Framework used for the characterization of the mode(s) of toxic action of the chemical substance under review has been incorporated into the recently-published version of U.S. EPA's cancer risk assessment guidelines. As such, it will be applied in all of the Agency's cancer risk assessments to determine if sufficient data exist to define the mode of action, and, if so, whether or not it would be expected to occur in humans. It also is being used as the basis for the ongoing updating of the 2001 IPCS Cancer Mode of Action Framework, and, thus, will be a key element in the cancer risk assessments prepared by WHO and IPCS.

C. Dissemination/training

Good choices by decision makers in industry and government must be supported by good science. Wise decision makers must be made aware of the science knowledge base and the tools that allow its integration into credible estimates of risk for the population they are charged to protect. ILSI has been at the forefront of organizations in providing education and training to those who must conduct risk assessments and to those who must make sense of and use them. Hundreds of people around the world, especially in developing countries, have benefited from the training opportunities that ILSI branches and RSI have offered. Some of these events have been done by ILSI alone; most have occurred in partnership with governments, FAO and WHO or other organizations. The impact of this collective effort may be difficult to measure, but one hopes it leads to the improvement and protection of the public's health.

IV. Future Directions for ILSI's Global Risk Assessment-Related Efforts

A. ILSI Strengths and Limitations

ILSI brings a number of strengths to its risk assessment-related efforts, including a reputation for scientific integrity, the global reach and perspective of its entities, and its ability to provide a neutral forum for discussions among scientists from academia, government, industry and the public interest/public health communities. ILSI also has the organizational flexibility to identify key issues and gaps in knowledge, and to move more quickly than is

often feasible in academic or governmental organizations to develop relevant research, risk assessment tools, and dissemination/training activities. These strengths provide ILSI with the potential to make a significant contribution toward reaching a better understanding of the scientific issues relevant to conducting a credible risk assessment.

It must also be mentioned that ILSI has limitations that will affect future risk assessment-related efforts. ILSI has activities in a wide array of scientific areas that merit continued attention and support; therefore, time, attention, and resources devoted to risk assessment must be balanced with commitments in other areas. Also, ILSI has only a finite number of in-house scientific and technical staff with relevant expertise. These realities mean that, to be most effective, efforts must be focused and must build on ILSI's unique strengths.

B. Strategic Focus: Continuous Improvement of Science-based Risk Assessment

This review of ILSI's risk assessment activities over the past five years or so reveals a wide variety of efforts in research, risk assessment tool/principle development, and dissemination/training. Although difficult to quantify, it is reasonable to conclude that these activities have contributed substantially to global efforts to improve the scientific bases of risk assessment and its value to good decision-making. These successes notwithstanding, many critical scientific issues remain and new ones are being identified. Some of the key topics that ILSI should remain or become involved in include:

1) Develop general principles for the adequate characterization of dose-effect relationships

This effort would serve to advance the state-of-the-science with regard to the nature of dose-effect relationships of human exposures to allergens, chemicals (both nutrients and others) and pathogens that may be present in food. Needless to say, whether or not *thresholds* for effects for representatives in each of the three categories remains a contentious-and still unresolved-issue. Among the questions to attempt to answer is "What constitutes reasonable evidence of the existence of a threshold for a specific chemical, microbe or nutrient?"

A project proposal currently is under development, at the request of the Strategic Issues Group. The goal of the project would be to develop a set of general principles by which a body of information would be considered adequate to describe the nature of a dose-effect relationship, including thresholds. A multi-step approach is envisioned, involving (1) data gathering, (2) convening of a Steering/Planning Committee, and (3) convening of an Expert Group to prepare the report. The Project Manager for this project should be someone representing an ILSI entity with prior experience on the topic (e.g., ILSI Europe or ILSI RSI).

2) Develop improved data and assessment tools which support the concomitant assessment of both the risks and benefits of consumption of specified food constituents.

One aspect of this issue is the determination of when does "enough of a natural constituent of food become 'too much?'" For example, when does the 'right' amount of the of fat in one's diet shift from the beneficial/minimal risk side of the equation to risk-of-concern side of the equation?

In addition, it has proven to be quite difficult to reach consensus on the content of advice developed for consumers of food products found to be contaminated with substances of concern. Consumption of the contaminants may confer risk, particularly to a fetus or young child. On the other hand, consumption of the food (e.g., fish) confers health benefit. The challenge is to achieve the proper balance between risk and benefit.

A possible ILSI project would be to develop side-by-side probabilistic risk/benefit assessments, using CARES. One could use well-worked and worn examples as case studies, such as mercury or PCBs in fish or organochlorine pesticides in milk, or identify examples that are less-well explored, more current (e.g., acrylamide), or brand new.

Example: As noted in Section II above, ILSI (and many other organizations) has given substantial attention in the past few years to the risk assessment of acrylamide residues in certain foods, with a lot of research undertaken to reduce the levels of acrylamide in foods. However, there has been less attention given to exposure assessment and the implications for human health of small amounts of other compounds formed during high temperature processes such as baking, frying or grilling of high carbohydrate foods.

The ILSI Europe Task Force (TF) in collaboration with ILSI NA and ILSI RSI published a review article focusing on exposure assessment and internal dose assessments of acrylamide in food, which contributed to the risk assessment of acrylamide in food and helped to understand the impact on public health. The article was provided to the FAO/WHO Joint Expert Committee on Food Additives (JECFA) for their evaluation of acrylamide in February 2005.

In 2005, the TF widened its scope from acrylamide to other heat processed compounds and changed its name to 'Process Related Compounds.' The mission of the TF is to maintain and improve public health by advancing the understanding of the magnitude and nature of effects of low-dose exposure to acrylamide and other potentially toxic compounds that may be formed during food processing in the human diet. The TF provides a neutral forum for exchange of information on these types of compounds. Although the TF will extend its activities from acrylamide to other compounds formed during high temperature processing of food, they will continue monitoring acrylamide activities, e.g. the EU Integrated Project HEATOX.

Example: ILSI Europe is also engaged in a project to *Investigate the Risk Benefit Analysis for Foods (BRAFO)*. The primary aim of this specific support action (SSA) is to develop a framework that allows for the quantitative comparison of human health risks and benefits in relation to foods and food compounds by expressing these on a common scale,

which takes account of quality of data and severity of effect. This will be based on the evaluation of changes in the quality/duration of life using a system that allows weighting of data quality and severity of effect, with quantification by QALY or DALY-like methodology. It is intended that the methodology developed is sufficiently transparent to serve as a reference for the harmonization of the evaluation methods used within the EU and more widely in international evaluation.

A methodology group will review and assemble the methodologies available; collaborate with three case study groups to integrate the methodological findings in their area and develop a framework applicable to a wide range of foods and food compounds. A total of three groups will review the literature to undertake a risk analysis, a benefit assessment, an exposure evaluation and quantitative net health impact assessment on three selected cases: Natural Foods (soy and fish); Dietary Intervention (folic acid and macronutrient replacement) and Heat Processing.

The criteria we have used to select examples are largely information dependent. Each of the proposed work packages concerns compounds or foods where reasonable data exists and where significant issues in risk/benefit are illustrated. The key deliverable of the program include the following main points:

- What risks might attach to a food, a food supplement, an additive or a contaminant?
- What benefits may accrue?
- What is the impact (severity) of these on quality and quantity of life?
- What is the quality of the data upon which these conclusions are based?

The principal outputs of this project will be:

- A full description of beneficial and adverse effects of our targeted food components and foodstuff intake across dose levels in the population at large. These examples are organized in three categories: natural foods, foodstuff used for dietary interventions, and heat processed compounds.
- A comprehensive framework that can be used to compare the quantitative and qualitative values of human health risks and benefits of compounds based on the same scale measurement.

These outputs will lead to the following benefits:

- Increased knowledge of the risk and benefits related to different categories of foods.
- A standardized common methodology for all case studies.
- The ability to compare directly the net health benefits of the selected examples
- Improved understanding of the qualitative and quantitative comparison of human health risks and benefits of compounds in foods
- A framework methodology that could be extended to take into consideration indirect health effects, economic, societal and environmental impacts.

3) The analysis of nutritional components of the diet, using CARES.

WHO recently announced that it would be convening an Expert Group to do such an analysis and then develop Risk Assessment Principles for Nutrients. As resources permit, the Expert Group would also be asked to develop international nutrient-specific Tolerable Upper Levels.

In 2003, the ILSI Research Foundation acquired an exciting new tool: the Cumulative and Aggregate Risk Evaluation System (CARES) software package. This tool, originally designed to conduct pesticide risk assessment, has the potential for application to other chemical-specific exposure scenarios, including nutritive components of the diet. Those who are working on ILSI's Global Strategy on Overweight and Obesity also appreciate its potential to enhance understanding of complex dietary patterns and their impact on body weight.

Some of the questions that could be addressed by ILSI include:

- 1) Given augmentation of common foods such as cereals and beverages with vitamins, minerals, and dietary components, are minimum dietary requirements being met, unmet or exceeded?
- 2) If requirements are underachieved, what foods are the best candidates for assisting in increasing intake of the desired component?
- 3) If requirements are being exceeded, what potential risk from over-consumption, if any, may exist?

As an example of what might be done to address some of these questions, ILSI Europe has established a task force which is examining the question of risk-benefit analysis, with initial emphasis on micronutrients. Traditionally, different approaches have been used to determine the recommended dietary allowances for micronutrients, above which there is a low risk of deficiency, and safe upper levels, below which there is a negligible risk of toxicity. The advice given to risk managers has been in the form of point estimates, such as the recommended dietary allowance (RDA) and the tolerable upper level (UL). In future, the gap between the two intake-response curves may become narrower, as more sensitive indicators of deficiency and toxicity are used, and as health benefits above the recommended daily allowance are taken into account. ILSI Europe has prepared a paper which reviews the traditional approaches and proposes a novel approach to compare beneficial and adverse effects across intake levels. This model can provide advice for risk managers in a form that will allow the risk of deficiency or the risk of not experiencing the benefit to be weighed against the risk of toxicity. The model extends the approach used to estimate recommended dietary allowances to make it applicable to both beneficial and adverse effects and to extend the intake-incidence data to provide a range of estimates that can be considered by the risk manager. The data requirements of the model are the incidence of a response at one or more levels of intake, and a suitable coefficient of variation to represent the person-to-person variations within the human population. A coefficient of variation of 10% or 15% has been used for established

recommended dietary allowances and a value of 15% is proposed as default for considerations of benefit. A coefficient of variation of 45% is proposed as default for considerations of toxicity, based on analyses of human variability in the fate and effects of therapeutic drugs. Using this approach risk managers, working closely with risk assessors, will be able to define ranges of intake based on a balance between the risks of deficiency (or lack of benefit) and toxicity.

As a follow-on, the proposed approach has been applied for a number of micronutrients for which significant subgroups in most European populations have intakes below nationally recommended levels, placing individuals at risk of suboptimal intake of important vitamins and minerals. The voluntary addition of micronutrients to the appropriate foods may help addressing the risks associated with low micronutrient intakes. However, since concerns need to be addressed regarding the potential for unacceptably high intakes, particularly for those people consuming very high large amounts of food, a theoretical model was developed based on the critical factors which determine the risk of unacceptably high intake for each micronutrient at high levels of food/energy intakes. These included (1) Tolerable Upper Intake Levels (UL), (2) high micronutrient intakes in Europe at the 95th percentile intake for each nutrient, (3) the proportion of fortified foods in the diets of individuals at the 95th percentile for energy intakes, (4) the proportion of foods to which micronutrients could practically be added, (5) a range of estimates for the fractions of foods which might be actually fortified for each nutrient. A maximum level was set up for each micronutrient per typical serving or 100 kcal portion. The outputs of the model were then compared against a recent model developed by AFSSA, based on the food intake data in France.

Three categories of micronutrients were identified, in which micronutrients could be added safely to foods at levels (per serving, e.g. 100 kcal) (1) greater than 1 European Commission Recommended Daily Intake (EC RDA): vitamin B12, vitamin C, vitamin E, riboflavin, panthotenic acid, niacin and thiamine; (2) between 50 and 100% of the EC RDA: vitamin B6, vitamin D, folic acid, biotin, copper, iodine and selenium; (3) between 10 and 40% of the EC RDA: iron, zinc, calcium, phosphorus and magnesium. A fourth category consisting of retinol, for which high end intake levels are close to UL for some population subgroups in Europe and thus requires further consideration.

The key conclusion of the exercise was that a wide range of vitamins and minerals can be added safely to foods at nutritionally important levels in the current diets of Europeans.

Similar efforts could be undertaken in other geographic localities, using data relevant to the local populations.

5) Continue and expand risk assessment training for relevant constituencies of the Branches

ILSI should commit to the conduct of at least one session per year per entity.

Appendix 3 provides a listing of risk assessment training and/or workshop sessions sponsored by ILSI entities over the recent past. These sessions may address, for example, "hot topics" of immediate concern (e.g., ILSI India's 2004 workshop on

pesticide residues in bottled water), topics of new or evolving interest (e.g., the development of new areas of regulatory interest) or the desire to introduce or review risk assessment principles, generally or specific to one area (e.g., chemical contamination, foodborne illness, etc.) because there has been a significant turnover in the decision-maker cadres in industry, government and/or academia of that region.

It is, of course, up to each entity to determine what the appropriate topic and who the appropriate "students" would be for any training session or workshop. The point made here is that each entity should specifically incorporate risk assessment training/workshops into their annual planning process. It should also be noted that no entity would be discouraged from holding more than one!

6) Continue to build and recognize science leadership: ILSI can contribute to strengthening research in risk assessment by providing fellowships or research support for young researchers in the field, sabbatical support to established researchers to work within ILSI entities, or support for the short-term placement of ILSI scientific staff in key academic research institutions for training and/or collaboration with leading scientists.

ILSI should consider re-establishing an external research program to be managed by the Research Foundation.

ILSI should provide sabbatical support for at least one scientist per year to work within an ILSI entity.

ILSI should provide support for at least one ILSI staff scientist per year to spend time in an academic research setting or relevant government agency.

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Appendix 1

Summary of Scientific Research Activities

TOPIC / Subtopic	COORDINATING ILSI ORGANIZATION	RESEARCH EFFORTS	MEETINGS	PUBLICATIONS	ILSI & NON-ILSI PARTNERS	KEY CONTACT(S)	KEY LEARNINGS
Risk Assessment-Chemical-Food Toxicology	ILSI North America	2001-2003: Technical Committee on Food Toxicology and Safety Assessment provided partial funding for an FDA-organized study on fumonisin-induced cardiovascular and atherogenic disease.			U.S. Food and Drug Administration	Catherine Nnoka, cnnoka@ilsi.org ; Steve Olin, solin@ilsi.org	The results from Stage 1 of the study were submitted to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for review
Risk Assessment-Microbial	ILSI NA	Studies (over a decade) on genetics of <i>Listeria monocytogenes</i> , assess if subtypes of this pathogen differ in their ability to cause human disease.			ILSI NA Technical Committee (TC) on Food Microbiology, Univ of Hawaii	Catherine Nnoka, cnnoka@ilsi.org	
Risk Assessment-Microbial	ILSI NA	Research projects on <i>Escherichia coli</i> O157:H7			ILSI NA TC on Food Microbiology, University, Univ of Georgia, Washington State Univ	Catherine Nnoka, cnnoka@ilsi.org	
Risk Assessment-Microbial	ILSI NA	3 projects on antibiotic resistance and risk to human health of farming practices			ILSI NA TC on Food Microbiology, Univ. of Tennessee at Knoxville, Health Canada, Univ of California	Catherine Nnoka, cnnoka@ilsi.org	

TOPIC / Subtopic	COORDINATING ILSI ORGANIZATION	RESEARCH EFFORTS	MEETINGS	PUBLICATIONS	ILSI & NON-ILSI PARTNERS	KEY CONTACT(S)	KEY LEARNINGS
Risk Assessment-Microbial	ILSI NA	4 research projects on <i>Listeria monocytogenes</i>			ILSI NA TC on Food Microbiology, GMA, Health Canada, Univ of Wisconsin, North Carolina State Univ, Cornell Univ	Catherine Nnoka, cnnoka@ilsi.org	

Appendix 2

Summary of Risk Assessment Tool/Principle Development Activities

TOPIC / Subtopic	COORDINATING ILSI ORGANIZATION	RESEARCH EFFORTS	MEETINGS	PUBLICATIONS	ILSI & NON-ILSI PARTNERS	KEY CONTACT(S)	KEY LEARNINGS
Risk assessment- General	ILSI North America		2005: ILSI NA annual meeting scientific session on Food Safety Considerations in Sensitive Subpopulations			Sharon Weiss, weiss@ilsi.org	
Risk assessment- Chemical- General	ILSI Brasil			August 2002 Regulation and Agro toxic Register – Approach of the Evaluation of Risk Exposure and Occupational Toxicological Risk			
Risk assessment- Chemical- General	ILSI Europe			Concise Monograph on Principles of Risk Assessment Related to Food and Water	ILSI RSI, WHO	Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	Provides the basic concepts and vocabulary of risk assessment.
Risk assessment- Chemical- General	ILSI Europe	2000-2001; six individual theme groups prepared review papers on hazard identification, hazard characterization, exposure assessment and epidemiology	June 2001: Plenary meeting to discuss draft papers	March 2002 Publication of Food Safety in Europe (FOSIE) Individual Theme Group Papers in Food and Chemical Toxicology	EC, ILSI RSI, OECD, WHO	Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	Papers serve as basis for the FAO/WHO update of the Principles and Methods for the Risk Assessment of Chemicals in Food.
Risk assessment- Chemical- General	ILSI Europe	Expert Group drafted integrated document on Risk Characterisation		Findings published in Food and Chemical Toxicology in February 2003	EC, WHO, ILSI RSI	Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	Papers serve as basis for the FAO/WHO update of the Principles and methods for the Risk Assessment of Chemicals in Food.

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Risk assessment-Chemical-General	ILSI Europe		Satellite symposia on Risk Assessment in Food: general principles and examples at Eurotox 2003, 28 September – 1 October 2003	Abstracts published in Toxicology Letters		Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	FOSIE results disseminated to a wide audience
Risk assessment-Chemical-General	ILSI Europe	Expert group developed draft guidance document for the safety assessment of botanicals and botanical preparations with use in food and food supplements	Workshop held in May 2002 to discuss draft guidance document	Revised guidance document published in the ILSI Europe Report Series and Food and Chemical Toxicology (2003) 41:1625-1649	ILSI North America	Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	Define science-based guidelines to evaluate the safety in use of botanicals
Risk assessment-Chemical-General	ILSI Europe	The Natural Toxin Task Force is currently actively developing a programme for a workshop to discuss the results of the EU project on Risk Assessment of Ochratoxin A	Organising Committee meeting will be held in October 2004 - Workshop anticipated June 2005	Summary report of the workshop to be published mid-late 2005	DG Research, EFSA, WHO to be contacted for involvement	Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	
Risk assessment-Chemical-General	ILSI Europe		September 2003. Workshop on tricothecenes with a special focus on Deoxynivalenol	Proceedings to be published in a Supplemental issue of Toxicology Letters October 2004		Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	Lay down the basis for a comprehensive risk assessment and contribute to the development of preventive strategies

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Risk assessment- Chemical- General	ILSI Europe	Expert group established to draft a guidance document (building on previous ILSI Europe activity) on structure-based thresholds for toxicological concern for substances present at low levels in the diet (pre-screening assessment to identify possible outliers)	Draft guidance document to be discussed at a workshop in March 2003	Revised document published in Food and Chemical Toxicology (2004) 41(1):65-83		Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	The concept is currently being used by JECFA in evaluating flavourings added to foods. The establishment of a more widely accepted TTC would benefit consumers, industry and regulators, by precluding extensive toxicity testing and safety evaluations when human intakes are below such a threshold. It would avoid valuable resources, costs and time being devoted to developing safety data and subsequent assessments of chemicals for which there are insignificant exposures, and contribute to reducing the use of test animals.

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Risk assessment-Chemical-General	ILSI Europe	The Threshold of Toxicological Concern Task Force engaged to draft a concise monograph on Threshold of toxicological concern (TTC): A tool for assessing substances of unknown toxicity present at low levels in the diet.	Concise Monograph planning meeting has been held and the first draft of the monograph is being prepared.	Publication of a Concise Monograph anticipated by Mid 2005		Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	To increase the awareness of the TTC concept and ultimately to gain wider acceptance of the principle. The TTC concept will be increasingly used by non-specialists, therefore it is essential to develop a simplified document ensuring that the concept is properly applied. The concept is considered to possess a lot of features that would be of interest to the general public especially the decrease in the use of animal testing and helping to focus resources on those compounds of most importance.
Risk assessment-Chemical-General	ILSI Europe	Expert Group to develop EU submission proposal for development of Risk Benefit Framework			Partners yet to be identified	Dr. Loek Pijls' lpijls@ilsieurope.be	- Link with EC Sixth Framework Projects HEATOX, SafeFood and SafeFoodNet - The Framework may be useful in Harmonising Risk benefit analysis (WHO and EFSA have expressed interest)

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Risk assessment-Chemical-General	ILSI Europe	Participation in EU funded project SafeFoodNet - to harmonise and integrate Accession Candidate Countries (ACC) structures and activities in the field of chemical food safety with those of Member States and to promote capacity building	A total of 5 workshops to be organised in 2005-2007		International Centre for Pesticides and Health Risk Prevention (ICPS) (Italy), coordinator of the project.	Dr. Loek Pijls' lpijls@ilsieurope.be	Better integration of Accession Candidate Countries with ongoing activities & bodies of the European Union (EU), contribute to implementation of food safety control systems equivalent to those in place within the EU, and guidance for the development of a system to collect dietary data which will be consistent and harmonised with what is being developed in the EU.
Risk assessment-Chemical-General	ILSI Europe	Expert Group to draft risk assessment framework for acrylamide		Publication expected mid- 2004	ILSI North America	Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	- Link with EC Sixth Framework Project HEATOX.. - The Framework may be useful for risk assessors, e.g. JECFA

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Risk assessment-Chemical-General	ILSI Europe	Expert groups convened to establish a framework for risk assessment of sewage sludge	<p>Poster session at IWA Biosolids Congress in Trondheim, June 2003</p> <p>Joint ILSI Europe/ECETOC workshop on organic contaminants in the soil planned in 2005</p>	<p>Publication of the conceptual framework submitted in Regulatory Toxicology and Pharmacology in October 2004</p> <p>Publication of the LAS case study expected in the same journal in the first half of 2005</p>	WHO	Bernard Bottex, E-mail: bbottex@ilsieurope.be	<ul style="list-style-type: none"> - WHO is a member of the expert group who prepared the document - Quick publication of the framework so that it can be taken into account for the revision of the EU Sludge Directive and by the DG Environment who opened a call for tender on "how to derive values for organic contaminants".
Risk assessment-Chemical-General	ILSI Europe	Expert group established to review how to assess quantitatively cancer risk from low-dose exposure to genotoxic carcinogens	Findings will be reviewed in a joint WHO, European Food Safety Authority (EFSA) and ILSI Europe workshop planned for 2005	Results of the expert group study will be published in a scientific journal by end 2004 or early 2005. Proceedings of the joint workshop will be published in late 2005 or early 2006	ILSI RSI, WHO (IPCS), EFSA	Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	Assess quantitatively cancer risk from low-dose exposure to genotoxic carcinogens and provide input to the EFSA group working on genotoxic carcinogens

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Risk assessment- Chemical- General	ILSI Europe	Food Chemical Intake Task Force is considering the use of retailers fidelity cards as a source of food consumption data to assess exposure to food chemicals. A pilot test with the colourant "sunset yellow" is being done.	Sept 2004 – Workshop	To be determined later		Bernard Bottex, E-mail: bbottex@ilsieurope.be	Task force in contact with the Exposure Assessment Working Group of EFSA's Scientific Committee in order to ensure complementary work. Discuss the possibility and limitations of a Pan-European Food Consumption Database
Risk assessment- Chemical- General	ILSI HESI	Ongoing – Emerging Issues Committee monitors, evaluates, and responds to emerging scientific issues and events relating to human and environmental health and safety, toxicology & risk assessment. Subcommittees established to explore research priorities and make recommendations to the HESI board on action areas.					

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Risk assessment- Chemical- General	ILSI HESI	Ongoing- collaborative experimental program conducted in laboratories worldwide with 4 working groups: hepatotoxicity, nephrotoxicity, genotoxicity, and a group addressing database development.		Compile and organize data from the three toxicity working groups into the ILSI Microarray Database.	ILSI HESI Application of Genomics and Proteomics to Mechanism-based RA Committee		
Risk assessment- Chemical- General	ILSI HESI	Ongoing – Developing standardized input data sets/data formats and then applying these data to existing aggregate risk models.		Generic data set have been made publicly available on the ILSI website.	ILSI HESI Risk Assessment Methodologies TC		
Risk assessment- Chemical- General	ILSI RSI	Ongoing-Establishment and management of Model Peer Review Center of Excellence	2003 - Peer review of Health Canada report on prioritization of genotoxic substances. 2004 - Developed concise summary of peer review responsibilities for decision-makers, including Sept 2004 review by external peer review panel.	Report to Health Canada - 2003. Publication of "Peer Review for Decision-makers" in early 2005.	EPA, Health Canada	S. Olin	
Risk assessment- Chemical- General	ILSI RSI		Feb. 2002-Training workshop on newly revised OECD test guidelines for acute oral toxicity	Training Manual	EPA, ICCVAM, Verband der Chemischen Industrie, Crop Life America, Health Canada, NTP, NIEHS, ITTLC	B. Julien S. Carter	

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Risk assessment-Chemical-General	ILSI RSI	Expert group developed state-of-the-science on use of non-cancer data in cancer risk assessment		"Use of non-cancer data in cancer risk assessment" published in Reg. Tox.Pharm., February 2003	EPA, Health Canada, API, ACC	S. Olin	Developed 15 principles for the use of data other than tumor counts in cancer risk assessment; case studies on benzene, butadiene, vinyl chloride
Risk assessment-Chemical-General	ILSI RSI	Develop further guidance on dose selection/data interpretation for chronic rodent bioassays, building on 1997 RSI publication	Expert Working Group Meetings - June 2002 through June 2004; Peer review workshop - early 2005	Publication in 2005	EPA, Health Canada	S. Olin	
Risk assessment-Chemical-General	ILSI RSI	Identify appropriate short-term assays/strategies for testing fibrous particles	Expert Working Group Meetings - March 2003 through February 2004	Publication in early 2005 of paper on "Testing of Fibrous Particles: Short-term Assays and Strategies"	EPA	S. Olin	
Risk assessment-Chemical-General	ILSI RSI	Addressing the question of the value and usefulness of screening assays to predict chemical toxicity, serve as early tiers in testing schemes, etc.	Expert Working Group Meetings, 2003, 2004; Poster presentation-SOT-March 2004; Symposium SRA - Dec. 2004	2005- Publication of report entitled "Framework for Use of Screening Tools in Context-based Decision-making" in peer-reviewed journal	EPA	I. Walls	Framework provides guidance to users on how to address specific questions related to minimizing human health risks in the event of exposure to potentially toxic chemicals.

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Risk assessment- Chemical- General	ILSI RSI	Developing analytical framework for evaluating human relevance of mode of action data; special case: PPARa agonist-induced rodent tumors	Peer Review Workshop - Dec. 2002 Symposium at SRA meeting - Dec. 2002 Symposium at SOT - Mar 2003	3 papers in November 2003 issue of Critical Reviews in Toxicology	EPA OPP, OPPT, ORD; Health Canada	D. Patton P. Fenner-Crisp	
Risk assessment- Chemical- General	ILSI RSI	"Testing" the Human Relevance Framework with non-cancer endpoints of toxicity and genotoxic carcinogens	2004-Peer review workshop	Publication in peer-reviewed literature in 2005	EPA OPP, OPPT; Health Canada	D. Patton P. Fenner-Crisp	
Risk assessment- Chemical- General	ILSI RSI	2002- Review available guidance on application of probabilistic methods to the assessment of operator exposure to agricultural pesticides		Report to EU, Early 2003	EU DG SANCO	B. Julien	There is a lack of scientific guidance; the review describes several key methodological questions that should be addressed.
Risk assessment- Chemical- General	ILSI RSI	2003-Evaluate methodological issues and data for probabilistic assessment of worker exposure to agricultural pesticides	November 2003- Peer review workshop, Brussels	Report to EU, November 2003; Submittal for publication in peer-reviewed journal, 2005	EU DG SANCO, EPA, PMRA-Health Canada, CalEPA-DPR, CLA, CLI, ECPA, NIOSH, USDA	B. Julien	Probabilistic analysis of handler exposure to pesticides is not yet ready for routine use. Underlying model structure needs improvement, methods for input distribution development are not adequately developed, areas of uncertainty are not accounted for.

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Risk assessment- Chemical- General	ILSI RSI	2003-Acquisition, management, updating and expansion of CARES®, a software tool for conducting aggregate and cumulative risk assessment for pesticides		2004- Version 2.0 available on ILSI RF website	ILSI HNI, CropLife America, EPA, ILSI RSI	B. Julien P. Fenner-Crisp	
Risk assessment- Chemical- General	ILSI RSI	Nanomaterial Toxicity Screening	Expert Working Group Meetings - February through May 2005	Publication in late 2005	EPA	J. Fitzpatrick	
Risk assessment- Chemical- General	ILSI South-Andean			2003 Translation into Spanish: ILSI Europe Concise Monograph on Risk Assessment Related to Food and Water. 2004 Publication (CDs)	ILSI South-Andean	MC. Cisternas	

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Risk assessment- Chemical-General	ILSI Southeast Asia Region	Provide information and discuss key issues on developing and improving FCS methodology, operational guidelines, advocacy for resources in response to various needs, including food safety exposure assessment data, and collaborative mechanisms for fostering further development and optimal uses of FCS data in developing countries. FAO updated development on FCS and food composition data development	1) January 25-26, 2003, Thailand- Food Consumption Surveys in Developing Countries- Issues and Challenges", 2) March 4, 2004, workshop on Food consumption survey and exposure assessment in conjunction with the 4th Asia Conference on Food and Nutrition Safety.	The workshop report has been submitted to be published at the UNU Nutrition Bulletin.	ILSI FAO Cooperative Framework, Institute of Nutrition, Mahidol University FAO, ILSI FAO Cooperative Framework, Bogor Agricultural University	Pauline Chan E Siong Tee	Workshop provided a platform for nutrition and food safety regulators and scientists to discuss interagency coordination on food consumption survey. A process to establish regional diets based on national food consumption for purpose of exposure assessment was also recommended. Follow up workshops will be organized to further the process towards harmonization of methods for dietary assessment.
Risk assessment- Chemical-Children's Health	ILSI HESI	Gathering of data on the use of behavioral testing for new drug and chemical risk assessment.		2003- Publication of "Neurobehavioral Assessment: Survey of Use and Value in Safety Assessment Studies" in Toxicol. Sci		D. Sandler	
Risk assessment- Chemical-Children's Health	ILSI HESI	Project to study the role of juvenile animal studies in assessments of pediatric safety of pharmaceuticals	November, 2003- Workshop			D. Sandler	

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Risk assessment-Chemical-Children's Health	ILSI HESI		June 2001 - Workshop on developmental immunotoxicology	Proceedings will be published in 2002	EPA	D. Sandler	
Risk assessment-Chemical-Children's Health	ILSI RSI	Project to develop a framework for assessing human health risks from exposure to chemicals during various developmental stages (conception to adolescence)	July 2001 - Workshop developed a Children's Risk Assessment Framework	Workshop report and 4 companion papers published in Environmental Health Perspectives, 2003-2004	EPA, Health Canada, ACC, CLA	S. Olin	Framework offers a process, questions, issues, and resources for assessing children's risks from chemical exposures
Risk assessment-Chemical-Children's Health	ILSI RSI	Case studies to test and refine the Children's Risk Assessment Framework	Expert Group began developing case studies to test and refine Framework; case studies to be completed in 2005	To be presented at EPA workshop in 2005, and published in 2005.	EPA, Health Canada	S. Olin	
Risk assessment-Chemical-Children's Health	ILSI RSI	Developing database with human physiological parameters for early life stages; evaluating and characterizing data for use in PBPK modeling	2003- Expert Group began populating database begun by EPA containing animal data	Series of papers to be published in 2005; release of publically-available, searchable database in the planning stages	EPA, Health Canada, ENVIRON	S. Olin	
Risk assessment-Chemical-Children's Health	ILSI RSI	Project to interpret guideline testing data on neurodevelopmental endpoints	2003-Steering Group met; 2004/2005-WG meetings; 2005-Peer Review Workshop; Symposium planned for 2005 Ann. Mtg of Teratology Society/ NBTS.	2005-Publication of findings in peer-reviewed journal	EPA OPP and OPPT	I. Walls	

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Risk assessment- Chemical- Children's Health	ILSI RSI	Project on direct dosing of pre-weaning mammals in toxicity testing that will develop a guidance manual on how to conduct this procedure	Working group meetings 2000 - 2003; Symposium at Teratology Society Annual Meeting - 2002	ILSI Press book- 2003	EPA	I. Walls	The book describes how to undertake direct dosing studies on pre-weaning mammals. This may be useful for ensuring the safety of infants exposed to toxic substances.
Risk assessment- Chemical- Children's Health	ILSI RSI	2002 - Project to evaluate approaches for screening drinking water contaminants for potential developmental toxicants	Summer 2002-WG began project scoping March, 2003-WG begins evaluation to determine value of existing (Q)SAR tools to predict developmental toxicity potential	September 2003- Workgroup report to sponsors; December 2004: Manuscript published in Birth Defects Research Part A.	EPA, Health Canada	B. Julien	The Working Group's report describes specific challenges in predictive modeling of this toxicity, and recommends two research efforts that will help inform the development of improved methodology.
Risk assessment - Chemical - Food additives	ILSI Brasil		August 30 - Seminar: "Update on Sweeteners"		ILSI Brasil	ilsibr@ilsi.org.br	Update on safety, uses and regulatory aspects.
Risk assessment- Chemical- Food Allergy	ILSI Brasil			2004 - Translation of ILSI Europe Concise Monograph on Food Allergy into Portuguese			
Risk assessment- Chemical- Food Allergy	ILSI Europe			Hypothesis paper on determination of a threshold level for allergenic foods by statistical analysis published in Allergy (2002) 57(8):741-746	Allergy Center Denmark	Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	Creation of a dose-response curve which enables the determination of a threshold dose which elicits an allergic

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							reaction in a given proportion of patients.
Risk Assessment-Chemical-Food Allergy	ILSI Europe			Concise Monograph on Food Allergy. Published July 2003		Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	Describe and clarify the differences between true food allergy and other adverse reactions in an overview for a broad audience given the growing public trend to ascribe any adverse reactions to food as an "allergy".
Risk assessment-Chemical-Food Allergy	ILSI Europe		ILSI Europe session on threshold for allergens at 9th Int. Symposium on Problems of Food Allergy, March 2004		ILSI HESI	Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	
Risk assessment-Chemical-Food Allergy	ILSI Europe	Expert Group set up in 2003 on Estimating Dose for Allergens	Scientific input and participation in the FARRP 4th meeting October 2004	Publication of a paper on a refined model threshold level for allergenic foods by mid 2005		Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	Contribute to the development of a mathematical model that can be used to calculate the proportion of the allergenic population who may react to any specified amount of a given allergen.

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Risk assessment- Chemical- Food Allergy	ILSI Europe	EG on Coeliac disease vs. wheat allergy for Determination of eliciting dose for both coeliac disease & wheat allergy		Article on wheat allergy & eliciting dose for coeliac disease. Publication expected end 2004.		Gillian Marmelstein, E-mail: gmarmelstein@ilsieurope.be	Review the feasibility of determining a common biomarker for both conditions and provide information on both issues, which are viewed as one by regulators.
Risk assessment- Chemical- Food Allergy	ILSI South-Andean			2004 Translation into Spanish: ILSI Europe Concise Monograph on Food Allergy. (requesting authorization)	ILSI South-Andean	MC. Cisternas	
Risk assessment- Chemical- Food Toxicology	ILSI South-Andean		2004 Conference on Food Toxicology		ILSI South-Andean- Pontificia Uiversidad Católica (Chile), member companies	J. Rozowski	
Risk Assessment- Chemical- Food Toxicology	ILSI North America		2004: Annual meeting scientific session on Heat Formed Compounds in Foods	2004: Abstracts available		Sharon Weiss, weiss@ilsi.org	

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Risk Assessment-Chemical-Food Toxicology	ILSI North America		2004: ILSI NA was part of a consortium of organizations responsible for organizing the meeting "Update: Scientific Issues, Uncertainties, and Research on Acrylamide in Food," Acrylamide II Workshop. ILSI NA was responsible for the working group on Toxicology and Metabolic Consequences		ILSI Risk Science Institute; Joint Institute for Food Safety and Applied Nutrition	Catherine Nnoka, cnnoka@ilsi.org ; Steve Olin, solin@ilsi.org	
Risk Assessment-Chemical-Food Toxicology	ILSI North America	2004: Subcommittee on Acrylamide is focusing on the development of a PBPK model to facilitate understanding of acrylamide metabolism and kinetics in humans and the application of this understanding in risk assessment. An expert working group was established.	2004: Acrylamide PBPK Modeling Working Group met at the National Center for Toxicologic Research		ILSI Risk Science Institute; National Center for Toxicological Research	Catherine Nnoka, cnnoka@ilsi.org ; Steve Olin, solin@ilsi.org	

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Risk Assessment-Chemical-Food Toxicology	ILSI North America		2004: Technical Committee on Food Toxicology and Safety Assessment provided financial support for the FARRP Third Scientific Roundtable in Elicitation Doses for Allergenic Foods: How Much is Too Much?		University of Nebraska, Food Allergy Research and resources Program; ILSI Europe	Catherine Nnoka, cnnoka@ilsi.org	
Risk Assessment-Chemical-Food Toxicology	ILSI North America		2003: Project Committee on Tolerable Upper Levels held workshop on Understanding Tolerable Upper Levels; participants included experts involved in setting TULs and government scientists and health professionals struggling with how to apply the TULs to improve public health		Publication is pending.	Michael Shirreffs, mshirreffs@ilsi.org	TULs were not meant to convey "toxic levels" and participants discussed the difficulty in assessing the health effects of consuming above the TULs on an acute, chronic, or lifetime basis.
Risk Assessment-Chemical-Food Toxicology	ILSI North America	2001-2003: Technical Committee on Food Toxicology and Safety Assessment provided partial funding for an FDA-organized study on fumonisin-induced cardiovascular and atherogenic disease.			U.S. Food and Drug Administration	Catherine Nnoka, cnnoka@ilsi.org ; Steve Olin, solin@ilsi.org	The results from Stage 1 of the study were submitted to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for review

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Risk Assessment-Chemical-Novel Foods	ILSI Europe	Expert group developed a draft guidance document on the safety assessment of novel foods and concepts to determine their safety in use	Draft document discussed at a workshop, 20-22 November 2002; Guidance document presented at the 10th International Congress on Toxicology, Tampere, Finland, July 2004.	Revised document published in Int. J. Food Sciences and Nutrition and in the ILSI Europe Report Series		Bernard Bottex, E-mail: bbottex@ilsieurope.be	Guidance document to be presented at the 10th International Congress on Toxicology, Tampere, Finland, July 2004. Provide guidance on what studies are appropriate and how these studies should be designed.
Risk Assessment-Chemical-Novel Foods	ILSI Europe	Update of an ILSI Europe publication in close collaboration with DG SANCO, to be translated in all the European languages and widely disseminated by the EC Services.		Update of the CM GM Technology and Food - Consumer health and safety (2002). This publication is being expanded with the new European regulation on GM food and feed. Publication expected end of 2005	European Commission-DG SANCO	Bernard Bottex, E-mail: bbottex@ilsieurope.be	Communicate how biotechnology can be applied to food, and how its safety assessment can be translated into the new European Regulation on GM food and feed.
Risk assessment-Chemical-Novel Foods	ILSI Europe	2004: two new activities on - History of Safe Use - Post Launch Monitoring (PLM) (Creation of an Expert Group to work on this issue)	Oct '03: Brainstorming meeting on History of Safe Use	Guidance paper that describes the practical application and use of this intuitive concept. To be published as an ILSI Europe Report beginning of 2005	Starting collaboration with ILSI NAFNSC Subcommittee on Post-market Adverse Event Monitoring for Foods	Bernard Bottex, E-mail: bbottex@ilsieurope.be	- Codification of the "history of safe use" concept. - Clarification of how and when PLM should be applied.

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Risk assessment- Chemical- Novel Foods	ILSI Europe		Creation of an Expert Group working on Post Launch Monitoring (PLM). The objective is to write a document that will give a definition of PLM, explain when it should be applied and when it should not, propose some guidance on how to apply PLM, what are the expected results and how to interpret them.			Bernard Bottex - bbottex@ilsieurope.be	Post Launch Monitoring is referenced in the European Union Novel Food Regulation (EC 258/97) – and by other national/international regulations. However there are no clear guidelines on what is expected from such studies, neither when nor how they should be carried out. This paper will clarify what can be expected from PLM.
Risk assessment- Chemical- Packaging Materials	ILSI Europe		November 2004 3rd Symposium on Food Packaging	2005- Publication of proceedings in Food Additives and Contaminants	EC DG SANCO, Public Health Agency of Barcelona, Univ. of Saragossa	Bernard Bottex, E-mail: bbottex@ilsieurope.be	Update on the state-of-the-art from a purely scientific point of view.
Risk assessment- Chemical- Packaging Materials	ILSI Europe			Reports on: 1) Polyethylene Terephthalate (2000) 2) Polystyrene (2002) 3) Polypropylene (2002) 4) Polyethylene (2002) 5) Exposure for Food Contact Materials (2002) 6) PVC (2003) 7) Paper and Board (2004) 8) Metal Packaging (2004)		Bernard Bottex, E-mail: bbottex@ilsieurope.be	Compilation of information regarding characteristics, uses, basic chemistry, safety and toxicology, regulations and environmental fate.

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Risk assessment-Chemical-Packaging Materials	ILSI Europe	Creation of an expert group that will be in charge of proposing guidelines on exposure assessment for food packaging materials: what information is needed, what are the gaps?	1st expert group meeting scheduled for end of 2004		ILSI North America Subcommittee on Packaging Materials	Bernard Bottex, E-mail: bbottex@ilsieurope.be	This activity will contribute to the work of for the European Food Safety Authority Additives & Food Contaminants Panel who is working on materials in contact with foods, as well as for the EC DG Sanco who is preparing the "super-regulation" on packaging materials.
Risk Assessment-Chemical-Packaging Materials	ILSI South-Andean		2004 Series of Presentations on Food Packaging		ILSI South-Andean, member companies	MC. Cisternas	
Risk Assessment-Microbial	ILSI Europe	Prepare activity proposal on 'Modeling tools for exposure assessment'				Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	- Identification of important areas for microbiological risk assessment that have impact on levels of cross-contamination
Risk Assessment-Microbial	ILSI Europe	Expert Group drafted report on Transmissible Spongiform Encephalopathies and the food chain		March 2003 Publication of ILSI Europe Report Series	The International Forum for TSE and Food Safety (TAFS)	Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	- Report has been endorsed by TAFS. - Contribute to the evaluation of the risk of transmitting BSE to animals or humans by products of bovine origin.

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Risk Assessment-Microbial	ILSI Europe	EG drafted report on foodborne parasites (Cryptosporidium, Cyclospora, Giardia)		Publication of ILSI Europe Report Series. June 2003		Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	- Worldwide interest in the report.
Risk Assessment-Microbial	ILSI Europe	Expert Group drafted report on foodborne viruses		September 2003 Publication of ILSI Europe Report Series + Accepted for publication in Intl. J. Food Microbiol.		Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	- Worldwide interest in the report.
Risk Assessment-Microbial	ILSI Europe			End of 2003 3rd edition of Concise Monograph HACCP		Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	
Risk Assessment-Microbial	ILSI Europe			End of 2003 Publication of report 'Incidence and importance of recontamination in microbiological risk analysis'		Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	- Report emphasises the importance of recontamination in microbiological risk assessment.
Risk Assessment-Microbial	ILSI Europe			Report on Mycobacterium paratuberculosis (MAP) expected in June 2004		Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	Identification of the food safety management systems that control MAP.
Risk Assessment-Microbial	ILSI NA		1993-2004: Technical Committee on Food Microbiology sponsors an annual symposia series at the annual meeting of the International Association for Food Protection (IAFP)	Abstracts from the symposia series are available each year.	International Association for Food Protection	Catherine Nnoka, cnnoka@ilsa.org	Annual symposia series focuses on emerging global issues in food microbiology

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Risk Assessment-Microbial	ILSI RSI	2002-Expert Panel review to consider risk-based approach to managing foodborne listeriosis.	Expert panel met 2003 / 2004; Presented symposium at 2003 IAFP; Presentation at AAAS 2004;	Publication expected in 2005	ILSI NA	I. Walls	Risk-based approach includes (1) preventing contamination of foods with Lm; (2) preventing growth of Lm to high numbers (3) science-based education messages targeted at susceptible populations and their caregivers
Risk Assessment-Microbial	ILSI RSI	2004- Expert panel review on shiga-toxin producing E. coli, including E. coli 0157:H7			ILSI NA	I. Walls	
Risk Assessment-Microbial	Risk Assessment - Microbial	2004-Develop approach for collection of global foodborne illness data useful for microbial risk assessments	Advisory committee met 2004.	Publication expected 2005. May be submitted to Codex Alimentarius.	IOC	I. Walls	Document lists minimum and optimum data sets for MRA, focusing on (1) data to determine burden of foodborne/ waterborne disease, (2) contamination of food/ water and (3) food consumption patterns.

Appendix 3

Summary of Dissemination/Training Activities

TOPIC / Subtopic	COORDINATING ILSI ORGANIZATION	RESEARCH EFFORTS	MEETINGS	PUBLICATIONS	ILSI & NON-ILSI PARTNERS	KEY CONTACT(S)	KEY LEARNINGS
Risk Assessment - Training-Workshops	ILSI Brasil	2004 Support for 6 scholarship researchers in the Government Toxicological Information and Assistance Center			ILSI Brasil and LACEN (Health Department)	ilsibr@ilsi.org.br	Background improvement.
Risk Assessment-Training/Workshops	FAO/ILSI Cooperative Framework		February 2003 Session on Food Safety at Asian Congress of Nutrition		IOC; FAO	S. Harris	
Risk Assessment-Training/Workshops	FAO/ILSI Cooperative Framework		2003 Regional Pre-Codex Workshop for Near East, Cairo, Egypt		IOC; FAO	S. Harris	
Risk Assessment-Training/Workshops	ILSI Argentina		May 13-15, 2002; May 6-8, 2003 5th and 6th Course on Quick and Automatized Microbiological Methods for Food Control	Course Manual on Quick and Automatized Microbiological Methods for Food Control.		Dr. Silvia Michanie	<ul style="list-style-type: none"> - Revising the new methodology for the detection of microorganisms and toxins - Revising the new trends in the hygiene and sanitation conditions - Application of the methodology in operations with HACCP and Good Manufacturing Practices

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Risk Assessment- Training/ Workshops	ILSI Argentina		August 12-13, 2002 FAO/ILSI/INTI Cooperative Framework Training Workshop on Risk Analysis for Mercosur Countries	Framework Training Workshop Manual on Risk Analysis for the Mercosur Countries. Our institution contributed to the assembly of this Manual	FAO, INTI (National Institute for Industrial Technology)	Dr. Clara Rubinstein	<ul style="list-style-type: none"> - Presentations by regional experts covered different aspects of the Risk Assessment process, from the scientific criteria involved to the problems of the LA region to access accurate information and develop their own databases and how to communicate risk analysis conclusions to their risk managers - Work groups were formed to discuss and solve specific cases related to the Risk Assessment of food additives, contaminants, pesticide residues

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Risk Assessment- Training/ Workshops	ILSI Argentina		September 16-19., 2002: Training Course on Detection Methods for Genetically Modified Organisms in the Food Chain	September 2002: Course Manual on The Detection Methods for GMO in the Food Chain	ILSI, USA; AACCC- American Association of Cereal Chemists, USA; JRC -Joint Research Center-, European Commission; INTA –National Institute of Agricultural Technology-, and SAGPyA – Agriculture Secretary-, ex-INASE, Argentina		Possibility of an active exchange of INTA professionals in charge of the GMO Detection lab. with the trainers and also with participants, many of which represented other governmental and industrial labs. -This interaction encouraged potential collaboration, participation in collaborative trials or ring test coordinate by JRC. Possibility of establishing a network of labs working in GMOs detection in Argentina (and possibly regionally).

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Risk Assessment-Training/Workshops	ILSI Argentina		August 25, 2003: Conference "Soybean in Human Nutrition" at the Argentine Biochemistry Foundation, Buenos Aires.		Health Ministry of Buenos Aires Province with the Institutional Sponsorship of the Argentine Biochemistry Foundation and La Plata University.		
Risk Assessment-Training/Workshops	ILSI Argentina		August 26, 2003: Conference "Soybean in Human Nutrition" at the Society of Pediatrics "Dr. Giannantonio" Education, Buenos Aires.				
Risk Assessment-Training/Workshops	ILSI Argentina		September 9 2003, Buenos Aires Workshop on Wheat Mycotoxins. The speakers were from INTI, INTA, Buenos Aires University and Industrial Representatives. The audience was a representative group of all the wheat and biscuits industry, including Kraft Foods Brazil.			Dr. Clara Rubinstein	Development of new practices in elimination of toxins both in the field and in the storage of wheat.

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Risk Assessment- Training/ Workshops	ILSI Argentina		October 20 2003 - Buenos Aires. Conference on Food Packaging.			Dr. Clara Rubinstein	<ul style="list-style-type: none"> - Sanitary and legislative aspects of the interaction of packaging and plastics with foods. - The new role of the active packaging. - And the challenge of the food packaging, in order to maintain the sensory properties of foods.
Risk Assessment- Training/ Workshops	ILSI Argentina		September 18 2003 - Buenos Aires Conference on "Food Allergens" With the dissertation of Dr. Michael Holsapple, ILSI HESI Director, Dr. María Estela Roux and Dr. Marín Quiroga Salcedo, both from Argentina.		SAN (Argentine Society of Nutrition)	Dr. Clara Rubinstein	<ul style="list-style-type: none"> - Experts in the different fields introduced basic concepts about immunology and the allergic response and gave an overview about the prevalence of food allergics among the population. - Dr. Holsapple talked about the process of allergenicity assessment for novel proteins.
Risk Assessment- Training/ Workshops	ILSI Argentina		September 19 2003 - Cordoba Conference on "Food Allergens" With the dissertation of Dr. Michael Holsapple, ILSI HESI Director, Dr. L. Vanella de Río Cuarto, from Córdoba, Argentina and Dr. Amuchastegui from San Juan, Argentina.		SAN (Argentine Society of Nutrition) Capítulo Córdoba	Dr. Clara Rubinstein	<ul style="list-style-type: none"> - Experts in the different fields introduced basic concepts about immunology and the allergic response and gave an overview about the prevalence of food allergics among the population. - Dr. Holsapple talked about the process of allergenicity assessment for novel proteins.

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Risk Assessment-Training/Workshops	ILSI Argentina		November 25, 2003 Conference: Selected Topic in Risk Assessment: GLP for non-clinical studies. Speaker: Dr. Nelida Mondelo, Gador Laboratories			Dr. Clara Rubinstein	- Developing of the regulatory toxicology to drugs of human use - GLP for non-clinical studies
Risk Assessment-Training/Workshops	ILSI Argentina		June 9, 2004: First International Conference about Sustainability Tools		National Technological University		
Risk Assessment-Training/Workshops	ILSI Argentina		June 24, 2004: ILSI Argentina participation in the Conference "Food Safety" as part of the 3rd Conferences Series on Food-Nutrition-Health organized by the Health Department of Buenos Aires Province in La Plata City				
Risk Assessment-Training/Workshops	ILSI Argentina		October 6, 2004: Conference "Biotechnology and Safety Evaluation: ILSI International Food Biotechnology Committee's (IFBiC) Projects"		ILSI's IFBiC - ILSI Argentina and SAGPYA: Food National Directorate and Office of Biotechnology with support from the Argentine Council for Biotechnology Information and Development	Dr. Clara Rubinstein	

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					(ArgenBio)		
Risk Assessment-Training/Workshops	ILSI Argentina		October 7-8, 2004: Workshop on Nutritional and Safety Assessments of Foods and Feeds Nutritionally Improved through Biotechnology		ILSI International Food Biotechnology Committee (IFBiC) and ILSI Argentina with the Institutional Sponsorship of the Secretary of Agriculture in collaboration with the Argentine Council for Biotechnology Information and Development (ArgenBio)	Dr. Clara Rubinstein	
Risk Assessment-Training/Workshops	ILSI Argentina		November 2004: Talk on Food Safety in Formosa Province				
Risk Assessment-Training/Workshops	ILSI Brasil		August 2003 Pesticides Risk Assessment				

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Risk Assessment-Training/Workshop	ILSI Brasil		2 training courses and Seminar on Microbial Risk Analysis		ILSI Brasil & PAS (convenio CNI/SEBRAE/SENAI/SENAC)	ilsibr@ilsi.org.br	Contribution to professional expertise
Risk Assessment-Training/Workshops	ILSI Europe		April 2003 Workshop on 'Impact of Food Safety Objectives on Microbiological Food Safety Management'	Publication of summary report February 2004 Proceedings expected mid-2004	ILSI RSI, FAO	Sandra Tuijelaars, Email: stuijelaars@ilsieurope.be	Contribute to the introduction of the FSO concept.
Risk Assessment-Training/Workshops	Focal Point in China		May 2002- Workshop on Microbial Risk Assessment		FAO	Junshi Chen	Led to start of nationwide microbial foodborne illness monitoring program
Risk Assessment-Training/Workshops	ILSI India		September 2003 SAARC Workshop on Food Safety, Goa, India		FAO/ILSI Cooperative Framework	R. Sinha	

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Risk Assessment- Training/ Workshops	ILSI India		28-29 October 2003- Workshop on Risk Assessment of Pesticide Residues in Water and Food		ILSI-India, ILSI RSI, Indian Toxicology Research Center and Indian Council of Medical Research	R. Sinha P. Fenner-Crisp	There is a need to create awareness about proper usage of pesticides to prevent contamination of food and water as also need to conduct more programs on risk assessment and create understanding in regulatory authorities and others about importance of science based decision making to prevent undue pressure on Government to adopt standards based on non scientific consideration. There is a need for proper surveillance and data collection on chemical and microbial contaminants.

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Risk Assessment-Training/Workshops	ILSI-India		Roundtable on JPC Findings on Pesticide Residues and Safety Standards in Soft Drinks, Fruit Juices and Other Beverages, New Delhi, India, March 19, 2004	Report	ILSI-India and RSI	Rekha Sinha Penny Fenner Crisp	The Joint Parliamentary Committee made a number of recommendations for restructuring the food control system and was not in favor of unscientific approach adopted by NGOs like CSE in dealing with issues of public importance. There is a role for ILSI .
Risk Assessment-Training/Workshops	ILSI-India		Second South Asian Workshop on Food Safety, Colombo, Sri Lanka, November 25-27		ILSI-India and FAO	Rekha Sinha Ezzedine Boutrif	
Risk Assessment-Training/Workshops	ILSI Japan		May 2002- Food Safety Symposium-Research and the cause and prevention of off-flavor with trichloroanisole from mold	Proceedings to be published in 2004	Food Industry Center	Fukitomi	
Risk Assessment-Training/Workshops	ILSI Japan		November 2002 Food Safety/Risk Assessment Workshop		ILSI RSI, NIHS, METI, Tokyo Metro-Hygiene Institute	Fukitomi	
Risk Assessment-Training/Workshops	ILSI Japan		August, 2003- Food Safety symposium on Research on detection methods for, and prevention of contamination by TAB	Publication in 2004	Food Industry, TNO	Fukitomi	

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Risk Assessment-Training/Workshops- Food Allergy	ILSI Korea		April 2003 1st Food Allergy Symposium	Meeting Proceedings	Korea Society of Food Immunology Research		
Risk Assessment-Training/Workshops	ILSI RSI		December 2003, March and April 2004- Presentation of Risk Awareness course to ILSI NA members		ILSI NA	D. Patton S. Olin I. Walls P. Fenner-Crisp	
Risk Assessment-Training/Workshops	ILSI RSI, ILSI Japan		Presentation of Risk Awareness course to ILSI Japan members and other relevant food safety regulators, 2004 Presentation of Risk Awareness course to (non-food) chemical regulators, in and outside of Japanese government, 2004 or 2005			P. Fenner-Crisp	

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Risk Assessment-Training/Workshops	ILSI NA		2004-2005: Short Course on Foodborne Illness Epidemiology, Surveillance, and Outbreak Investigation. The Technical Committee on Food Microbiology is organizing a one-day course on foodborne illness epidemiology, surveillance, and outbreak investigation.			Catherine Nnoka, cnnoka@ilsi.org	The program for this course will include lectures and exercises on epidemiological techniques and current foodborne pathogen surveillance systems, laboratory techniques and existing laboratory surveillance systems for foodborne pathogens, and mock outbreak investigations.
Risk Assessment-Training/Workshops	ILSI NA		2003: Technical Committee on food Microbiology organized PulseNet Training for Food Industry Scientists - a special workshop to familiarize food industry scientists with PulseNet, CDC's molecular subtyping network for foodborne bacterial disease surveillance.		Centers for Disease Control and Prevention (CDC), Virginia's State public health laboratory, the American Association of Public Health Laboratories		The committee is continuing this partnership to improve scientists' ability to control and prevent foodborne diseases, and enhance our ability to respond rapidly and effectively to microbial threats to the safety of our food supply.
Risk Assessment-Training/Workshops	ILSI NA		2003-2004: ILSI NA "101" Course on Risk Assessment for Nutritionists and Food Scientists			Pameal Copeland, pcopeland@ilsi.org; Regina Randall, rrandall@ilsi.org	

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Risk Assessment- Training/ Workshops	ILSI Southeast Asia Region	<p>Facilitate information exchange for reviewing and exploring consensus on scientifically-based improvements for ASEAN food safety standards to bring these in line with Codex standards - FAO assisted with program development.</p> <p>A database will be developed to incorporate the 10 ASEAN countries' food safety standards and GSFA to provide updates at regular interval and track the harmonization progress.</p> <p>*FAO updated developments on JECFA and Codex GSFA</p>	<p>1) March 4-5 2002, Singapore- 1st Workshop on ASEAN Food Safety Standards Harmonization</p> <p>2) December 17-18, 2002, Malaysia- 2nd Workshop on ASEAN Food Safety Standards Harmonization- focus on colors, sweeteners, preservatives</p> <p>3) December 10-11, 2003 - 3rd ASEAN Food Safety Standard Harmonization workshop - focus on flavors; progress report on colors, sweeteners, and preservatives</p>	<p>Reports of workshops available.</p> <p>ASEAN- Codex Food Safety Standard database (for updating and tracking on harmonization efforts towards Codex GSFA)</p>	<p>1) FAO Codex/Food standard Div, WHO food Safety Dept, ILSIFAO Framework, ASEAN Secretariat</p> <p>2) ILSI FAO Cooperative Framework, Malaysia Ministry of Health, Standard and Quality Division</p> <p>3) ILSI FAO Cooperative Framework, Indonesia Nat Agency for Drug & Food Control</p>	<p>Boon Yee Yeong Veronita Rusli</p>	<p>The 10 ASEAN countries are able to share information and build consensus on progress, and to adopt and harmonize their food safety standards towards Codex GSFA systems and standards. Currently have reviewed color, sweeteners, preservatives and flavors.</p> <p>Countries have agreed to contribute towards a common database to be housed at ILSI SEA Region. The database will have limited access through the ILSI Website.</p>

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Risk Assessment-Training/Workshops	ILSI Southeast Asia Region	Enhance the technical expertise of regional regulators in utilizing the process of risk analysis and its three component to ensure a safe food supply. Will address how risk analysis can be applied to the regional situation using relevant case studies and hands on exercise	March 4, 2004 Satellite Workshop on Global Risk Analysis Manual Training in conjunction with the 4th Asia Conference on Food and Nutrition Safety, Indonesia		ILSI FAO Cooperative Framework, FAO, WHO	Boon Yee Yeong Veronita Rusli	
Risk Assessment-Training/Workshops	ILSI Southeast Asia Region	The conference theme "Emerging Food and Nutrition Safety Issues – Impact on Science, Health and Economics" will focus on safety issues along the farm to fork continuum. Six Plenary session will cover issues on Microbial, mycotoxins, chemical contaminants, water quality and safety, safety assessment of nutrients and non-nutrients added to food and challenges of new technology .	March 2-4 , 2004 4th Asia Conference on Food and Nutrition Safety, Bali, Indonesia	Proceedings will be published	ILSI FAO Cooperative Framework, Bogor Agricultural University, ILSI RSI, ILSI Branches, IFBiC, Indonesian Association of Food Technologists, and National Agency of Drug and Food Control	Boon Yee Yeong Veronita Rusli	Raised awareness on the importance of risk analysis for food safety for Asia countries, share research efforts on food safety in the region and to encourage developing countries to participate at Codex Regional meetings

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Risk Assessment-Training/Workshops	ILSI Southeast Asia	To update regulators on science-based information used for chemical and microbial risk assessment/risk analysis	September 2002, Malaysia Pre-Codex Meeting		FAO/ILSI Cooperative Framework	Boon Yee Yeong Veronita Rusli	
Risk Assessment-Training/Workshops	ILSI Southeast Asia	Promote and coordinate use of sound science in risk assessment to facilitate food safety decision making. Facilitate understanding of risk analysis process and assist with development of food safety control system in Indonesia	November 27-28, 2002, Indonesia Seminar and Workshop on Food Safety Risk Assessment		FAO/ILSI Cooperative Framework, WHO, ILSI RSI. Ministry of Health Indonesia, Bogor Agricultural University		
Risk Assessment-Training/Workshops	ILSI South Africa		September 2003 Southern Africa Regional Meetings on Modernizing Food Control Systems		ILSI-FAO Cooperative Framework	A. Mackenzie	