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# Future Direction of Utilization of NGS in Microbial Analysis in Food Industry

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**<Summary>**

More than ten years have passed since the next generation sequence (NGS) appeared. The use of next-generation sequencing has made it possible to read DNA sequences at an extremely high speed and at low cost, as compared to the conventional Sanger method. The technologies brought about by NGS in the food industry can be roughly divided into two methods: a method of determining the entire genome sequence of one single bacterium from a colony and a method of extracting genomes of various microorganisms directly from food. Both technologies will bring a different landscape to the food industry.

In the past ten years, especially in the latest five years, the progress of research on genome sequences from colonies has been remarkable. In particular, the application of food poisoning bacteria in the molecular epidemiology field is being performed at a remarkable speed. Such a technology is not only applied to the molecular pidemiological analysis of food poisoning conducted by public organizations, but also widely applicable to the food industry. On the other hand, the method of extracting genomes of various microorganisms directly from food, in particular, 16S rRNA amplicon sequencing has made it possible to analyze bacterial flora at a much faster speed than culture methods. There is great potential in the future, especially in the fields of food quality control and raw material control.

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# MiFuP Safety: A Database Service for Finding Genes Associated with Harmful Functions in Microbial Genome Sequences

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**<Summary>**

In order to support the safe and proper use of microbes, NITE Biotechnology Center （NBRC） developed and has provided a web-based database service, called MiFuP Safety since December 2017, which is dedicated to the search for microbial genes associated with harmful functions. This service aims at assessing hazardous properties of a given microbe based on its genome sequence, taking advantage of the current state of technology where the cost of genome sequencing is much lower than in the past.

MiFuP Safety searches for bacterial genes associated with harmful functions such as toxin production and antibiotic resistance based on the genome sequence of a given microbe, and estimates the potential harmfulness of the microbe. For this purpose, the database defines two sets of criteria, one for the identification of functional genes based on their molecular properties such as sequence similarity and conservation of a specific domain/motif compared to known proteins, and the other for the detection of gene combinations required for the expression of harmful functions. Users have only to submit nucleotide or amino acid sequences of the microbe to be assessed, including whole genome nuclotide sequences, and then the database automatically searches for genes associated with harmful functions registered in the database, and provides predicts of the potential harmfulness of the microbe based on the presence or absence of registered genes or set of genes.

This database service enables users, even without any bioinformatics knowledge, to get information about hazardous properties of the target microbe from its genome sequence easily and quickly. We hope this database will be widely used as an important tool for safety assessment of microbes in use and those detected on the factory production lines.

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# Development of Chemical Toxicity Prediction System (AI-SHIPS) Using Toxicity Related Big Data

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**<Summary>**

This project (construction of AI-based Substances Hazard Integrated Prediction System: AI-SHIPS) was started in 2017 as a development project for energy-saving electronic device materials evaluation technology by the Ministry of Economy, Trade and Industry. Now in its third year, results continue to steadily accumulate. This project is a computational scientific method based that assumes use of a 28-day repeated dose toxicity test on rats, which is a frequently used screening toxicity test under the Chemical Substances Control Law (hereinafter referred to as the CSCL). We aim to develop a toxicity prediction system in silico over five years (from 2017 to 2021).

By developing this forecasting system, we plan to reduce the development time and cost related to safety assessment, which is said to account for 20% of the research expenses for developing new chemical substances and functional chemicals in Japan. This is expected to improve R&D capabilities as well as efficiency. At the same time, the use of this system is expected to improve the safety evaluation ability of chemical manufacturers, and reduce risks from chemical substances.

We are developing this prediction system based on the expression mechanism of molecular biological toxicity using extremely high quality GLP data. In early stages of the research, we will focus on developing methods for predicting hepatotoxicity, nephrotoxicity and blood toxicity, while at the same time work on PBPK prediction and metabolite prediction model development, etc. In this research, we aim to construct an integrated toxicity prediction system for chemical substances. This paper outlines the background and purpose of this project as well as the current development status.

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# A Physiologically Based Pharmacokinetic Model to Predict Chemical Concentrations in Livers after Virtual Oral Doses

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**<Summary>**

Current methods for estimating the health risks of chemicals require guideline animal testing studies. Consequently, only a small fraction of chemicals possesses adequate data for assessing potential hazards. This fact highlights the urgent need to develop more efficient and informative toxicity determination tools. It is generally accepted that in vitro high-throughput screening assays combined with computational models might provide a suitable alternative to traditional animal testing studies. The aim of the present study was to evaluate absorption rates (caco-2 cell permeability) and model the plasma and hepatic pharmacokinetics of approximately 50 disparate types of chemicals after virtual oral administrations in rats based on reported rat plasma values and experimental pharmacokinetics determined after oral administration to rats. The current study employed a simple onecompartment model recently recommended by US authorities as a high-throughput toxicokinetic model and a simple physiologically based pharmacokinetic (PBPK) model consisting of a chemical receptor compartment, a metabolizing compartment, and a central compartment. To ensure the diversity of chemical structures in the original chemical space, the chemical structures described by 196 chemical descriptors were calculated by a chemoinformatics tool using 50,000 randomly obtained molecules. The resulting chemical space was then projected onto a two-dimensional plane for visualization using generative topographic mapping methods. An inverse relationship was observed between no-observed-effect levels (NOEL) after oral administration and chemical absorbance rates evaluated for cell permeability ($r = –0.98$, $p < 0.001$, $n = 17$). The plasma concentration curves and the maximum concentrations of a varied selection of approximately 30 chemicals obtained by high-throughput toxicokinetic models and our simple PBPK models were consistent. However, the hepatic and plasma concentrations or the areas under the concentration–time curves of approximately 50 chemicals were different between the PBPK modeling and empirically obtained values. Although the numbers of compounds were limited in the present study, lowest observed effect level (LOEL) values for hepatoxicity from the Hazard Evaluation Support System Integrated Platform (HESS) in Japan and the areas under the hepatic concentration–time curves (AUC) estimated using PBPK modeling were inversely correlated ($r = -0.78$, $p < 0.05$, $n = 7$). This study provides important information to help simulate the high hepatic levels of potent hepatotoxic compounds. The present models could estimate the relationships between plasma/hepatic concentrations of chemicals and drugs after oral doses using both forward and reverse dosimetry with a view to predicting hepatic toxicity as a part of chemical risk assessment.

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# The Transition of Operation of the Type 1 Usage Regulation Examination at the Research and Development Stage in Japan and Its Evaluation as an Applicant Viewpoint

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**<Summary>**

The confined field trials (CFT) in the research and development of living modified plants (LMP) have been discussed in the international meetings, such as the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety. On the Japanese legal framework of the biosafety on LMP centering on the Cartagena Law, the permission was obligated basically by the same examination procedure, regardless of the research purpose, the industrial purpose, and the scale of implementation. Clearing the regulations was a burden for researchers, and there were few cases in which researchers implemented CFT for genetically modified plants in Japan. However, in recent years, the operation of approval examination of Type 1 Usage Regulations at the examination research stage in the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and Ministry of Environment (MoE) has been eased, and it is expected to facilitate the carrying out CFT in earlier stage of research and development of LMP by academic researchers. In this report, we would like to introduce the transition of the operation of the Type 1 Usage Regulation Examination at the research and development stage by MAXT and MoE during this 15 year after enforcement of the Cartagena Law, as an applicant viewpoint.

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# E＜ Research Institute of ILSI Japan Members ＞
# The Nisshin OilliO Group's R&D

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**<Summary>**

As a leading company in the field of edible oils, the Nisshin OilliO Group conducts research and development aimed at the creation of values to enrich people's lives by harnessing the three natural powers possessed by plants—that is, the power to improve flavor, the power to enhance health and the power to elevate beauty.

We are utilizing the oil and fat technology that we have nurtured over many years to discover solutions to customer needs and issues. In our commercial-use business we are developing functional oils aimed at providing solutions that are tasty, healthy and easy to use. In our processed oil and fat business we are promoting the development of products that realize the taste and qualities demanded by customers. And in our household-use business, in accordance with changes in people's lifestyles, we are creating values and markets for new edible topping oils that can be sprinkled directly on food for consumption.

We are also polishing our proprietary technologies that serve as the foundation for value creation, including the development of new-structure oils and fats, such as crystallized powder fats, acoustic texture evaluation technology, and observational research of the behavior and attitudes of consumers. Furthermore, we seek to contribute to the promotion of good health through dietary habits in various stages of life by, for example, deepening our nutritional research of medium-chain triglycerides (MCTs) and their qualities and developing dysphagia diet food products.

The new Research and Development Center, which was launched at the end of 2016 at the Yokohama Isogo Plant, the Nisshin OilliO Group's largest production site, aims to promote workstyle reform through a concentrated onefloor open-plan design, to accelerate R&D in laboratories arranged by function, and to enhance presentation functions. Based on this Research and Development Center, we intend to speed up innovation and create new values together with various stakeholders.

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# ILSI Japan Biotechnology Research Committee: Workshop on Application of Data Transportability in ERA of Genetically Modified Plants

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**<Summary>**

ILSI Japan Biotechnology Research Committee held ERA workshop in May, 2016 and invited ERA experts from Japan, U.S. and Australia at the workshop. Also, the Committee held ERA study meetings in November, 2016 and April, 2018 to contribute further progress of science based ERA through review of a current concept of environmental risk assessment in Japan and discussion on data transportability of confined field trial data. Based on the discussion in these workshops and study meetings, “Application of Data Transportability in ERA of Genetically Modified Plants” was held at Bellesalle Yaesu on November 7th, 2018. ERA experts from U.S. Europe and Argentina were invited to the workshop and introduced purpose and significance of confined field trials (CFTs) and examples of data transportability in the country/region. Also, summary of an analysis of CFTs for three GM events across sites in different climate zones outside Japan are introduced. From Japanese speakers, a concept of ERA of GM crops in Japan, a concept of data transportability and its status in Japan are presented as a first topic. Next, recent activities on data transportability of CFTs in ILSI Japan was introduced. Total of 73 people participated the workshop from industry, academia and regulators and conducted an active discussion during QA sessions and panel discussion. During the panel discussion, ERA experts from U.S. Europe and Argentina confirmed that it is important for data transportability of CFTs to be conducted in multiple environments and well designed.

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# The Workshop on Safety Assessments for Highly Purified Food/Food Additives Produced with Genetically Modified Microorganisms

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**<Summary>**

The workshop on " The Workshop on Safety Assessments for Highly Purified Food/Food Additives produced with Genetically Modified Microorganisms." sponsored by ILSI Japan Biotechnology Research Committee was held on March 18, 2019 at the Meiji University Surugadai Campus. 47 people from industry, authorities and academia participated in the workshop.

In Japan, safety examination for food and additives produced with recombinant DNA technology has been obligated since April 2001, and for Highly Purified Food Additives such as amino acids, safety examination as HRF has been done from 2005, and over 40 items have published as Highly Purified Food Additives till the date.

The Workshop was only for the safety evaluation of Highly Purified Food/Food Additives from the scientific point of view, and active discussions were held through lectures, questions and answers, and panel discussions.

After the discussion among us, an important consensus point was shared from the fact-based issues that we have a chance to discuss about the equivalency assessment / analytical sensitivity for the trace of impurities on the safety assessment of Highly Purified Food Additives. The applicant, and the Ministry of Health, Labor and Welfare (MHLW), and the Food Safety Commission (FSC) should continue to debate scientifically, for the clarification of the scientific logicalness to guarantee the safety assessment. .

In addition regarding Highly Purified Food, we could share specific issues such as implementation of the security and the need for voluntary standards.

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# Report of the 51st Session of the Codex Committee on Food Additives

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**<Summary>**

The Codex Committee on Food Additives (CCFA) held its 51st Session in Jinan, China, from 25th to 29th March, 2019. More than 250 food safety regulators were from 48 Member countries, European Union and 33 nongovernment international organizations.

The followings were the major agenda in this Session: (1) Codex General Standard for Food Additives, (2) Alignment of the food additive provisions of commodity standards and relevant provisions of the GSFA, (3) International Numbering System (INS) for Food Additives, and (4) Proposal for additional and changes to the priority list of substances proposed for evaluation by JECFA. The consensus included alternative notes to advance solutions on sweeteners by starting to phase out existing references to Note 161.

The next 52nd Session would be scheduled in China from 2nd to 6th March, 2020.