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Problems of the Japanese Standards for the Risk Assessment of GMOs

A preliminary study by the Codex Study Group[1], Tokyo

In order to protect consumers from the potential risks of genetically modified organisms (GMOs), it is essential for food regulators to have effective ways to assess the risks. The Japanese food safety administration, however, falls short of ensuring consumer confidence mainly due to the following deficiencies:

1. The Food Safety Commission, which carries out genetically modified (GM) food risk assessment in Japan, is a part of the public administration and is not independent of the government.
2. Consumer representatives are not included among the members of the Food Safety Commission.
3. With regards to public disclosure of information, concealment of information is easily carried out citing industrial secrets and patents as excuses for non-disclosure.
4. The Food Safety Commission does not function so as to critically examine or confirm data submitted by companies for risk assessment purposes.
5. An in-country CODEX commission has not been established.
6. The only means for linking the actions of the Japanese Government in the various working groups of the CODEX Commission with Japanese citizens is a liaison council, and the opinions of consumers expressed in this council are frequently ignored by the government.
7. For risk communication, the opinions of Japanese citizens are solicited through the internet and so on, but how these are actually reflected, or not reflected, in policies remains the arbitrary decision of bureaucrats. There is insufficient explanation of the reasons why opinions are not reflected in policy.

In particular, in January 2004, the Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants) were revised in order to harmonize with the Codex Principles for the Risk Analysis of Foods derived from Modern Biotechnology (General Principles) and the CODEX Guideline for the conduct of Food Safety Assessment of Food Derived from Recombinant-DNA Plants (Plant Guideline). From our point of view, the CODEX standards themselves contain some inadequacies, but compared with CODEX standards, the Japanese standards contain far more deficiencies. Below we list the main problems of the Japanese standards.

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[1] The Codex Study Group consists of consumers, researchers and journalists including NGO delegates to the Codex ad-hoc Intergovernmental Task Force on Biotechnology that took place in Japan from 2000 to 2003 and from 2005 to 2007. The group is working to lobby the government, for example, by sending comments to the Codex liaison council in Japan. This report was written as a preliminary study for an international survey on the risk assessment of GMOs. For more information, please contact: ryoko-s@prics.net

Unexpected effects

A holistic approach and application of the precautionary principle are necessary when dealing with unexpected effects arising from genetic modification.

It is well known that genes do not manage the bodies and functions of organisms in isolation from one another, but work together in a complex network of mutuality. It is extremely difficult to predict what will occur within the body of the organism when genes from different species are inserted into a gene network. The greatest concern of consumers regarding the safety of GM food is that unexpected changes occur in the food due to genetic modification and that these will have an adverse effect on their health.

The CODEX Plant Guideline makes a distinction in unintended effects between "predictable" effects and "unexpected" effects, citing the following actions as the means to hold these "unexpected" effects to the absolute minimum.

+ knowledge of the inserted trait and its metabolic connections or of the site of insertion
+ molecular biological techniques and biological techniques

Further, there is mention of improved preventative measures for "unexpected" effects in the future, which are in the realm of wishful thinking, as follows.

+ Expanding information on plant genome,
+ Increased specificity in terms of genetic materials introduced through recombinant-DNA techniques compared with other forms of plant breeding.

The Japanese standards contain two references to the prediction of the effects of modification.

In the first reference it is stated that, "changes in the properties of genetically modified foods (seed plants) are sufficiently predictable by scientific means," and that this is one of the two conditions that make safety assessment possible (Chapter 1, Section 4). The following are cited as the concrete means of the prediction.

+ knowledge of the properties of the inserted DNA (gene),
+ and knowledge of the changes in the genome into which the gene has been inserted.

Further, it is stated (Chapter 1, Section 4-3) that, "For this safety assessment, sufficient data or information should be available to minimize the risk of unpredicted adverse effects on human health caused by genetically modified foods (seed plants)." The following are cited as the concrete means of carrying this out.

+ Toxicological analysis,
+ Nutritional analysis.

In both of the references in the Japanese standards, the extremely ambiguous expression 'sufficient' is used as the criterion for the assessment ruling, what constitutes 'sufficient' being left to the arbitrary judgment of the risk assessor.

Both the CODEX and Japanese standards, besides the trait/property of the inserted gene itself, take as the object of the risk assessment only the narrow range of effects of the inserted gene on the site of insertion or the genome, and this is based on the reductionism that each gene merely carries out its functions independently.

In order to protect the health of consumers from the adverse unexpected effects of genetic modification, how the organism as a whole, including the gene network and factors other than the genes, reacts to the gene insertion must be confirmed before the product is marketed. At the very least, long-term nutritional trials on large animals, including humans, are necessary. In addition, in the case of signs that indicate a risk, in conformity with the precautionary principle, it is necessary that the product is not marketed before safety is confirmed.

CODEX GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS	**Japanese Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants)**
16. Unintended effects due to genetic modification may be subdivided into two groups: those that are "predictable" and those that are "unexpected". Many unintended effects are largely predictable based on knowledge of the inserted trait and its metabolic connections or of the site of insertion. Due to the expanding information on plant genome and the increased specificity in terms of genetic materials introduced through recombinant-DNA techniques compared with other forms of plant breeding, it may become easier to predict unintended effects of a particular modification. Molecular biological and biochemical techniques can also be used to analyse potential changes at the level of gene transcription and message translation that could lead to unintended effects.	**CHChapter 1 General Provisions** **Section 4** **Principles and basic concepts for safety assessment of genetically modified foods (seed plants)** Safety assessment is feasible only when changes in the properties of genetically modified foods (seed plants) are sufficiently predictable by scientific means from the properties of the inserted DNA (gene) and the changes in the modified genome, and when sufficient comparison can be conducted between the host and recombinant plants.
17. The safety assessment of foods derived from recombinant-DNA plants involves methods to identify and detect such unintended effects and procedures to evaluate their biological relevance and potential impact on food safety. A variety of data and information are necessary to assess unintended effects because no individual test can detect all possible unintended effects or identify, with certainty, those relevant to human health. These data and information, when considered in total, provide assurance that the food is unlikely to have an adverse effect on human health. The assessment for unintended effects takes into account the agronomic/phenotypic characteristics of the plant that are considered in total, provide assurance that the food is unlikely to have an adverse effect on human health. The assessment for unintended effects takes into account the agronomic/phenotypic characteristics of the plant that are typically observed by breeders in selecting new varieties for commercialization. These observations by breeders provide a first screen for plants that exhibit unintended traits. New varieties that pass this screen are subjected to safety assessment as described in Sections 4 and 5.	**Chapter 1 General Provisions** **Section 4** **Principles and basic concepts for safety assessment of genetically modified foods (seed plants)** 3 The safety assessment of genetically modified foods (seed plants) will be conducted in terms of all changes in the traits expected to be added to the seed plants. For instance, inserting a DNA sequence not only confers a specific trait to the plant (intended effect) but also may also confer additional traits or eliminate or modify the existing traits of the host (unintended effects). These unintended effects may be harmful, beneficial or neither harmful nor beneficial to the growth of the host plant or for the safety aspects of the genetically modified foods. Nevertheless, the effects of the intended and unintended addition of traits or changes in traits should be individually assessed from toxicological and nutritional viewpoints, while the assessment of the safety of the foods should also be conducted from the global viewpoint. For this safety assessment, sufficient data or information should be available to minimize the risk of unpredicted adverse effects on human health caused by genetically modified foods (seed plants).

Post-market Monitoring

Follow-up surveys are necessary to monitor effects that appear after the product goes on sale.

Nevertheless, it is not possible to eliminate all risks from "unexpected effects". Putting GM foods on the market despite this risk is tantamount to carrying out living-body human experiments on consumers concerning "unexpected effects". Monitoring is therefore indispensable for swift recognition of adverse post-market health effects in order to take preventive measures against the spread of harmful health impacts.

On this point, the CODEX Plant Guideline states (paragraph 6) that, "Risk management measures such as post-market monitoring of consumer health effects may assist the risk assessment process," and the General Principles, thought to be the grounds for this, refer to the possibility of epidemiological surveys on human health impacts being in some cases appropriate means of risk management concerning post-market monitoring for the purposes of "verifying conclusions about the absence or the possible occurrence, impact and significance of potential consumer health effects" (Paragraph 20-A).

As a result of limiting the role of the Food Safety Commission to risk assessment, however, Japan's safety assessment standards contain no statement concerning "risk management".

Further, the CODEX General Principles include mention of labelling and product tracing as means of risk management (Paragraph 21), and thus if the CODEX standards were to be strictly applied a labelling system based on traceability, as in the EU, should be possible, but the Japanese standards contain no reference to this, and the Ministry of Health, Labour and Welfare, which carries out risk management, applies mandatory labelling only to a limited number of genetically modified foods.

The Japanese consumer is eating more than anyone else in the world of the world's most widely cultivated GM crop, GM soy. Implementation of monitoring should be carried out particularly for the Japanese consumer.

CODEX GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS	**Japanese Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants)**
SECTION 1 SCOPE 6. Risk management measures such as post-market monitoring of consumer health effects may assist the risk assessment process. These are discussed in paragraph 20 of the Principles for the Risk Analysis of Foods derived from Modern Biotechnology. **Principles for the Risk Analysis of Foods derived from Modern Biotechnology** 20. Post-market monitoring may be an appropriate risk management measure in specific circumstances. Its need and utility should be considered, on a case-by-case basis, during risk assessment and its practicability should be considered during risk management. Post-market monitoring may be undertaken for the purpose of: A) verifying conclusions about the absence or the possible occurrence, impact and significance of potential consumer health effects; and B) monitoring changes in nutrient intake levels, associated with the introduction of foods likely to significantly alter nutritional status, to determine their human health impact.	**no provisions for post-market monitoring**

Donor organism DNA

Assessment of donor organism anti-nutrients are not required under Japanese safety assessment standards.

The CODEX plant guideline states that the donor organism that is to be considered is "the donor organism(s) or other closely related members of the family" (Paragraph 26), and that as well as pathogenicity or toxin production, other traits (e.g. anti-nutrients) are seen as important. (It is particularly important to determine if the donor organism(s) or other closely related members of the family naturally exhibit characteristics of pathogenicity or toxin production, or have other traits that affect human health (e.g. presence of anti-nutrients).)

The Japanese standards, however, define donor organisms very narrowly, without the expression "other closely related members of the family", and makes do with the very simplistic expression concerning the donor organism that "the pathogenicity or toxin production are unknown", or in the case that they are known that "the inserted DNA itself does not produce toxin(s), or that the proteins arising from the inserted DNA are non-pathogenic" (Chapter 2, Section 5-1 (2)). The expression stating that the pathogenicity or toxin production is "unknown" rather than "non-existent" cannot be overlooked. Based on the CODEX Plant Guideline Paragraph 36, the burden of proof may be placed upon the applicant, but because of the way the Japanese standards are phrased, "unknown" could be grounds for evasion of responsibility. Further, in the Japanese standards there is no mention of other traits of the donor organism (e.g. presence of anti-nutrients) despite the fact that these are considered as important in the CODEX guideline.

CODEX GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS	**Japanese Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants)**
DESCRIPTION OF THE HOST PLANT AND ITS USE AS FOOD	Chapter 2 Standard for the Safety Assessment of Recombinant Seed Plants as Foods [Genetically Modified Foods (Seed Plants)]
26. Information should be provided on the donor organism(s) and, when appropriate, on other related species. It is particularly important to determine if the donor organism(s) or other closely related members of the family naturally exhibit characteristics of pathogenicity or toxin production, or have other traits that affect human health (e.g. presence of anti-nutrients). The description of the donor organism(s) should include: A) its usual or common name; B) scientific name; C) taxonomic classification; D) information about the natural history as concerns food safety; E) information on naturally occurring toxins, anti-nutrients and allergens; for microorganisms, additional information on pathogenicity and the relationship to known pathogens; and F) information on the past and present use, if any, in the food supply and exposure route(s) other than intended food use (e.g. possible presence as contaminants).	Section 5 Inserted DNA, gene products and expression vector construction 1 Donor of the inserted DNA (2) Safety - The donor of the inserted DNA should not be known to show any pathogenicity to humans or produce toxins. Moreover, if any pathogenic strain is known within the donor species, as in the case of E. coli, it should be indicated that the donor has been derived from a non-pathogenic strain. - If the donor has been reported to be pathogenic or to produce a toxin, it should be demonstrated that the inserted DNA itself does not commit to produce any toxin, and that the protein(s) derived from the inserted DNA is non-pathogenic. - It should be clear whether the donor of the inserted gene has a history of safe consumption.
SAFETY ASSESSMENT Expressed Substances (non-nucleic acid substances) Assessment of possible toxicity 36. Information should be provided to ensure that genes coding for known toxins or anti-nutrients present in the donor organisms are not transferred to recombinant-DNA plants that do not normally express those toxic or anti-nutritious characteristics. This assurance is particularly important in cases where a recombinant-DNA plant is processed differently from a donor plant, since conventional food processing techniques associated with the donor organisms may deactivate, degrade or eliminate anti-nutrients or toxicants.	

Impacts on population groups (differences in dietary culture or geography) or sub-groups

Impacts are likely to differ according to differences in dietary culture, age and so on. There is no consideration of this in the Japanese standards.

At present, the approval of food additives is carried out using different standards in each country, and one of the reasons stated for this is that intake levels vary with differences in dietary culture. This is an important aspect that, in general, is indispensable in risk management, and can also be applied to GM foods. Intake levels differ not only with dietary culture, but also between adults, foetuses, infants, and children.

In the CODEX Plant Guideline, it is stated that intake levels differ between dietary cultures, regions, age groups, sexes and so on, and that because impacts differ, population sub-groups should be taken into account. For example, Paragraph 49 of the Plant Guideline states that, "Attention should be paid to the particular physiological characteristics and metabolic requirements of specific population groups such as infants, children, pregnant and lactating women, the elderly and those with chronic diseases or compromised immune systems," indicating that detailed assessments are required.

The Japanese standards, however, make no reference to this. This implies that there is no notion, philosophy or culture of taking population groups into account concerning food intake in the Japanese standards.

The consumption of soybeans by Japanese people is high compared with the countries of Europe and America, and this should probably be taken into consideration. In the future, as global movements of people increase, it will perhaps be necessary to heighten consideration for differences in ethnicity and dietary culture.

CODEX GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS	**Japanese Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants)**
DESCRIPTION OF THE HOST PLANT AND ITS USE AS FOOD 25. The history of use may include information on how the plant is typically cultivated, transported and stored, whether special processing is required to make the plant safe to eat, and the plant's normal role in the diet (e.g. which part of the plant is used as a food source, whether its consumption is important in particular subgroups of the population, what important macro- or micro-nutrients it contributes to the diet). SAFETY ASSESSMENT Expressed Substances (non-nucleic acid substances) Assessment of possible toxicity 35. The safety assessment should take into account the chemical nature and function of the newly expressed substance and identify the concentration of the substance in the edible parts of the recombinant-DNA plant, including variations and mean values. Current dietary exposure and possible effects on population sub-groups should also be considered. Nutritional Modification 49. Information about the known patterns of use and consumption of a food, and its derivatives should be used to estimate the likely intake of the food derived from the recombinant-DNA plant. The expected intake of the food should be used to assess the nutritional implications of the altered nutrient profile both at customary and maximal levels of consumption. Basing the estimate on the highest likely consumption provides assurance that the potential for any undesirable nutritional effects will be detected. Attention should be paid to the particular physiological characteristics and metabolic requirements of specific population groups such as infants, children, pregnant and lactating women, the elderly and those with chronic diseases or compromised immune systems. Based on the analysis of nutritional impacts and the dietary needs of specific population subgroups, additional nutritional assessments may be necessary. It is also important to ascertain to what extent the modified nutrient is bioavailable and remains stable with time, processing and storage. 52. Because of geographical and cultural variation in food consumption patterns, nutritional changes to a specific food may have a greater impact in some geographical areas or in some cultural population than in others. Some food plants serve as the major source of a particular nutrient in some populations. The nutrient and the populations affected should be identified.	no provisons

Toxicological assessment of proteins and non-protein substances in the GM organism

In Japan, the toxicological assessment is extremely simple and is based on substantial equivalence

In the CODEX Plant Guideline, it is stated that oral toxicity studies may need to be carried out in cases where the GM protein present in the food is not similar to proteins that have previously been consumed (Paragraph 38). Further, in the case of non-protein substances that have not previously been safely consumed in food should be assessed through studies on metabolism, toxicokinetics, sub-chronic toxicity, chronic toxicity/carcinogenicity, reproduction and development toxicity according to the traditional toxicological approach (Paragraph 39).

Further, the CODEX Plant Guideline states that the new substance from the recombinant-DNA plant may be isolated and compared with the substance involved that has been synthesized in terms of its structure and function (Paragraph 40).

The Japanese standards place the "daily intake of protein" at the centre of safety assessment, and simply give the content of safety assessment as whether or not the "significant amount" has been exceeded. There is also no mention of non-protein substances (Chapter 2, Section 6-3).

However, if we look at the experiments of Dr Irina Ermakova (Institute of Higher Nervous Activity and Neurophysiology of Russian Academy of Sciences) in 2005[2], and the research (2005) of Vanessa E. Prescott et al.[3] in Australia showing that transgenic expression of a plant protein (α-amylase inhibitor-1 from the common bean) in a non-native host (transgenic pea) led to altered structure and immunogenicity, it is clear that there is a necessity for harmful impacts of proteins to be examined very carefully, and that the Japanese judgement only on the basis of "significance" is insufficient.

[2] http://www.oeko.de/oekodoc/277/2006-002-en.pdf

[3] *J. Agric. Food Chem.*, **53** (23), 9023 -9030, 2005. 10.1021/jf050594v

CODEX GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS	**Japanese Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants)**
SAFETY ASSESSMENT Expressed Substances (non-nucleic acid substances) Assessment of possible toxicity 38. In the case of proteins, the assessment of potential toxicity should focus on amino acid sequence similarity between the protein and known protein toxins and anti-nutrients (e.g. protease inhibitors, lectins) as well as stability to heat or processing and to degradation in appropriate representative gastric and intestinal model systems. Appropriate oral toxicity studies3 may need to be carried out in cases where the protein present in the food is not similar to proteins that have previously been consumed safely in food, and taking into account its biological function in the plant where known. 39. Potential toxicity of non-protein substances that have not been safely consumed in food should be assessed on a case-by-case basis depending on the identity and biological function in the plant of the substance and dietary exposure. The type of studies to be performed may include studies on metabolism, toxicokinetics, sub-chronic toxicity, chronic toxicity/carcinogenicity, reproduction and development toxicity according to the traditional toxicological approach. 40. This may require the isolation of the new substance from the recombinant-DNA plant, or the synthesis or production of the substance from an alternative source, in which case, the material should be shown to be biochemically, structurally, and functionally equivalent to that produced in the recombinant-DNA plant.	Chapter 2 Standard for the Safety Assessment of Recombinant Seed Plants as Foods Section 6 Recombinant plant 3 Daily intake of the gene product (protein) and its significance The ratio of the daily intake of the gene product to that of the total protein in humans should be estimated. In principle, the intake of the product protein should not account for a significant portion of the daily total protein intake. If it is significant, scientific rationales should be presented to demonstrate that it does not affect human health. —to demonstrate the absence of any problem associated with inactivation of the antibiotic, based on the amount of consumption of the expressed protein (the enzyme catalyzing the antibiotic), and the digestion by artificial gastric or intestinal fluid and reduction by cooking (e.g. heating) described in Section 6-4-(3).

Differences in Agricultural Methods (Herbicides)

Concerning the appearance of herbicide tolerant GM crops, there is a necessity for full safety assessments to be carried out.

The use of specific herbicides has increased due to the appearance of herbicide tolerant GM crops. There is a necessity to carry out a full safety assessment of these changes in agricultural methods.

On this point, the CODEX Plant Guideline states concretely that, "e.g., procedures for assessing the human safety of chemicals" should be applied (Paragraph 54). Further, with respect to a comparative analysis of "key components", "a further comparison with the recombinant-DNA plant grown under its expected agronomic conditions may need to be considered (e.g. application of an herbicide)," (Paragraph 44), drawing attention to the fact that differences in growing conditions may lead to differences in composition.

However, in the case of the Japanese standards, the section equivalent to the CODEX standard above, Chapter 1, Section 4-5, does not go into as much detail as the CODEX standards do, and in the clause concerning comparison of cultivation method in Chapter 2, Section 6-9, there is no mention of agricultural chemical use.

CODEX GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS	**Japanese Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants)**
POTENTIAL ACCUMULATION OF SUBSTANCES SIGNIFICANT TO HUMAN HEALTH 54. Some recombinant-DNA plants may exhibit traits (e.g., herbicide tolerance) which may indirectly result in the potential for accumulation of pesticide residues, altered metabolites of such residues, toxic metabolites, contaminants, or other substances which may be relevant to human health. The safety assessment should take this potential for accumulation into account. Conventional procedures for establishing the safety of such compounds (e.g., procedures for assessing the human safety of chemicals) should be applied.	Chapter 1 General Provisons Section 4 Principles and basic concepts for safety assessment of genetically modified foods (seed plants) 5 Some recombinant plants may exhibit traits (e.g. herbicide tolerance) which may indirectly cause accumulation of pesticide residues, altered metabolites of such residues, toxic metabolites, contaminants, or other substances which may be relevant to human health. These possibilities should also be considered in the safety assessment.
Compositional Analyses of Key Components 44. Analyses of concentrations of key components5 of the recombinant-DNA plant and, especially those typical of the food, should be compared with an equivalent analysis of a conventional counterpart grown and harvested under the same conditions. In some cases, a further comparison with the recombinant-DNA plant grown under its expected agronomic conditions may need to be considered (e.g. application of an herbicide). The statistical significance of any observed differences should be assessed in the context of the range of natural variations for that parameter to determine its biological significance. The comparator(s) used in this assessment should ideally be the near isogenic parental line. In practice, this may not be feasible at all times, in which case a line as close as possible should be chosen. The purpose of this comparison, in conjunction with an exposure assessment as necessary, is to establish that substances that are nutritionally important or that can affect the safety of the food have not been altered in a manner that would have an adverse impact on human health.	Chapter 2 Standard for the Safety Assessment of Recombinant Seed Plants as Foods Section 6 Recombinant plant 9 Methods for cultivation - Information on how different the recombinant plant is from the host in terms of cultivation methods should be described. In principle, there should be little difference. If there is any difference, scientific rationales should be presented to demonstrate the safety of the recombinant plant. - Usages of agricultural chemicals (e.g., pesticides and herbicides) should be described. - In cases where the recombinant plant is tolerant to a herbicide by catalyzing it, its metabolites should be identified, and the safety of the major metabolite should be confirmed.

Working towards elimination of antibiotic resistance genes

The Japanese standards take as their point of departure the perception that antibiotic resistance marker genes are safe

Concerning the use of antibiotic resistance marker genes, the CODEX Plant Guideline states that in the future, when alternative transformation technologies that do not result in antibiotic resistance marker genes in foods become available, then these "should be used" (Paragraph 55), a cautious position on the use of antibiotic resistance marker genes that indicates a stance that is positive towards changes in techniques. The CODEX Plant Guideline states that in the case that "the presence of the antibiotic resistance marker gene or gene product" indicates risks to human health, they "should not be present in the food", and that "Antibiotic resistance genes used in food production that encode resistance to clinically used antibiotics should not be present in foods." (Paragraph 58) This is because of the concern that antibiotic resistance marker genes that enter the human body can impart antibiotic resistance to pathogenic bacteria and may result in adverse impacts on the treatment of illnesses.

The Japanese safety assessment standards, on the other hand, state optimistically that, "The safety assessment of the currently used antibiotic resistance markers such as the kanamycin-resistance gene has been appropriately conducted, and there have been no safety concerns to date." (Chapter 1, Section 4-9) Further, it is necessary to point out that the fact that an assessment has been appropriately conducted does not necessarily guarantee safety itself. Regarding the changeover to alternative trait transformation technologies that do not use antibiotic resistance marker genes, the Japanese standards also state that those technologies "should be considered for use" (Chapter 1, Section 4-9), which does not really positively encourage the changeover. In the "Items concerning the properties inserted DNA or gene (including the antibiotic resistance marker gene) and gene products" (Chapter 2, Section 5-2 (4)), there is no mention of the risks or concrete prohibitive conditions stated in the CODEX standards.

CODEX GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS	**Japanese Standards for the Safety Assessment of Genetically Modified Foods (Seed Plants)**
55. Alternative transformation technologies that do not result in antibiotic resistance marker genes in foods should be used in the future development of recombinant-DNA plants, where such technologies are available and demonstrated to be safe. 58. If evaluation of the data and information suggests that the presence of the antibiotic resistance marker gene or gene product presents risks to human health, the marker gene or gene product should not be present in the food. Antibiotic resistance genes used in food production that encode resistance to clinically used antibiotics should not be present in foods.	Chapter 1 General Provisions Section 4 Principles and basic concepts for safety assessment of genetically modified foods (seed plants) Chapter 1 General Provisions Section 4 Principles and basic concepts for safety assessment of genetically modified foods (seed plants) 9 The safety assessment of the currently used antibiotic resistance markers such as the kanamycin-resistance gene has been appropriately conducted, and there have been no safety concerns to date. However, in the future development, alternative transformation methods that do not result in any residual antibiotic resistance genes in food should be considered to use, where such techniques are available and demonstrated to be safe. 10 Along with the continuing progress in the recombinant DNA technology, these standards should be revised as required.