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Risk Assessment Manual for Chemical Hazards in Agricultural and Animal-Originated Foods

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Foreword

Agricultural and animal-originated foods are threatened of their safety by a number of external factors arising from various stages and processes, such as production, forwarding, butchery and processing/ distribution/ storage. Chemicals, which can affect safety of agricultural and animal-originated foods in their production stage, that is, the stage of crop cultivation or livestock keeping, include pesticides, veterinary drugs and environmental contaminants. Risk assessment is a process to assess toxicity of these substances, to calculate persistence of these substances in foods or environment and exposure to human body, and thus to evaluate their impact on human body and the degree of risk. Risk assessment results are used as a basis for food safety policies to set NOAEC and HBGL of chemicals, residue limit to prevent human body exposure and residue test criteria.

In line with industrial advancement and industrialization of agricultural, stockkeeping and fisheries businesses, the possibility of exposure to chemical hazards in production and processing stages is increasing gradually. In addition, as international trade of food ingredients is accelerating, more scientific and global-standard risk assessment techniques must be developed and utilized to secure safety of agricultural and animal-originated foods.

'Risk Assessment Manual for Chemical Hazards in Agricultural and Animal-originated Foods' describes basic principles and methods of chemical hazard assessment in foods by reflecting international risk assessment trends as much as possible. It also describes risk assessment techniques for veterinary drugs and environmental contaminants by substance.

These techniques have been updated through comprehensive analysis on risk assessment guidelines and methods recommended by the U.S. and the E.U. as well as CAC (CODEX) and FAO/ WHO (JECFA, Joint FAO/WHO Expert Committee on Food Additives, and JMPR, Joint FAO/WHO Meeting on Pesticide Residues).

We hope that 'Risk Assessment Manual for Chemical Hazards in Agricultural and Animal-originated Foods' will be of assistance to risk assessment, risk management and risk communication officers and related persons in understanding basic principles and procedures of risk assessment and learning the detailed methods and also contribute to securing reliability and consistency of risk assessment results, increasing safety of agricultural and animal-originated foods and globalization of risk management operation.

Authors,

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Contents

1. Risk Analysis on Chemical Hazards in Agricultural and Animal-originated Foods

Human beings take foods to obtain energy necessary in growth and maintaining health. Chemicals in foods are divided into nutrients as natural constituents and exogenous chemical substances, such as food additives, toxins, contaminants and agricultural and veterinary chemicals. Chemicals, such as food additives and agricultural and veterinary chemicals, play an important role in production and distribution of foods. Food additives are used to increase food productivity as they increase keeping quality or flavor of foods and agricultural pesticides and veterinary drugs increase resistance of crops and livestock against diseases and pests. Environmental contaminants that exist in the course of food production, processing and distribution are generated by various human activities. Discharged into the environment, these contaminants are unintentionally flown into foods in the course of food production, manufacturing, processing and distribution. These contaminants trigger damages to human health when existing in amounts larger than the prescribed. Therefore, these chemicals are called hazardous chemicals or chemical hazards.

Toxicity, the negative impact chemical hazards exert on human health, varies widely according to structure, absorption and metabolic characteristics of the respective chemicals. Nervous system abnormality, carcinogenicity, genomic damage and teratogenesis are representative symptoms caused by chemical hazards.

To verify chemical characteristics and toxicity of chemical hazards and to identify the amounts of toxicity generation are important in securing safety of foods from chemical hazards.

For chemical hazards in foods, it is advisable to block the source of generation first. However, in case the use of a substance in foods is inevitable, economic value generated by the use is considerably higher than the estimated level of risk and residues can be kept below a level harmful to human body through application of an appropriate regulatory means, establish regulations, such as on the amount of use, method of use, period of use and acceptable amount of use in foods, while permitting use of the respective substance. Once a use is banned or regulatory means for the conditions of use are implemented, it is necessary to check the implementation status.

The test on the amounts of contamination or residues in foods is a process to check whether or not the amount of substance existing in foods is below a level to be of hazard to human health.

Risk assessment on chemical hazards is a series of operations to set an amount of target substance that does not exert negative impact on human health on the basis of scientific information. In other words, it is to set acceptable daily intake (ADI) or tolerable daily intake (TDI) and maximum residue limit (MRL) of the substance in foods. Risk assessment serves as a basic axis of risk analysis.

For risk analysis on foods, the three operations of risk assessment, risk management and risk communication are organically connected so as to improve consistency, scientific value and sequential decision-making in the field of food safety. Risk analysis on chemical hazards in foods is carried out by establishing management plans and measures to ensure health of food consumers and to reduce chemical hazard residues and contamination based on the results of scientifically conducted risk assessment and by exchanging various opinions with consumers and other related persons.

1-1. Risk Analysis Process

Risk analysis consists of risk assessment, which is to check risk on human health caused by exposure to food-originated hazards and to scientifically evaluate occurrence probability of such risk, risk management, which is to decide and implement a policy with a goal to minimize risk occurrence on human body predicted on the basis of the results of risk assessment, and thus to evaluate the results of the policy implementation, and risk communication, which is to exchange various opinions with consumers and other related persons on the basis of organic integration between risk assessment and risk management.

Risk Assessment: Risk assessment consists of four stages, which are hazard identification, hazard characterization, exposure assessment and risk characterization. It is conducted based on scientific, specialized and statistical knowledge and information.

Risk Management: Functionally separated from risk assessment, risk management is a process of politic decision making and of management on items completed of the decision based on the results of risk assessment. Appropriate protection and handling measures are selected by compositely reviewing all factors relating to the protection of human health, economic conditions, such as trade increase, and cultural conditions including eating habits.

Risk Communication: Risk communication refers to the entire process of information and opinion exchange and communication with and between not only risk assessors and risk managers, but also consumers, industry, academic circle and other related groups.

1-2. Interaction between Risk Assessment and Risk Management

In execution principles described in Section V. Risk Analysis of Procedural Manual, Vol. 18, 2008, CAC recommends to functionally separate risk assessment and risk management in order to ensure scientific completeness of risk assessment, to avoid confusion about the roles of risk assessor and risk manager and to reduce conflict of interests. Successful risk analysis is based on functional separation between risk assessment and risk management. In addition, importance of communication, such as exchange of opinions between risk assessor and risk manager is being emphasized for the purpose of establishing the range of risk analysis, deriving and formulating problems and developing risk profile. Moreover, necessity of risk assessment can be determined in the stage of problem formulation and risk profile preparation.

1-3. Problem Formulation

This is a pre-stage for risk assessment. Problem formulation is to establish risk assessment strategies by considering opinions of risk assessor, risk manager and stakeholders in order to decide the necessity of risk assessment and the range of assessment and by examining impact of a chemical substance subject to assessment on food safety, possibility of risk on the related groups, impact from economic viewpoint, consumers' awareness about the risk, risk occurrence possibility by population group and advantages of using the substance in foods.

In the course of problem formulation, it is particularly important to exchange opinions with other related persons (companies and stakeholders that have information about the substance concerned). When formulating a problem, it is necessary to compare all food safety-related problems, and thus to establish relative priorities among the problems, to set up risk assessment strategies and to check all relevant factors in deciding admittable risk level and risk management options. In problem formulation, ① information risk manager seeks to obtain from the results of risk assessment is specified, ② data required for risk assessment and data that can be used in risk assessment are listed and ③ risk assessment schedule is proposed.

1-4. Risk Profile

Risk profile is prepared for the purpose of specifying characteristics of chemical hazards and their harmfulness to human body by analyzing risks that can be caused by chemical hazards in foods and also to provide information about risk management options. In other

words, it provides sufficient information on issues concerning food safety and solutions with which risk managers can promptly decide on management options when problems occur. This is a risk assessment at an earlier phase, which is to preferentially suggest all elements concerning risk at the time of assessment. Risk profile contains a brief description of a hazard together with information on situations and products associated with the hazard, predicted problems, potential results, consumers' awareness and the related risks and benefits (regarding human health and economic issues). In addition, risk profile is used to decide assessment priorities of a substance for risk assessment, assessment items and whether or not risk assessment is necessary.

In general, the cases in which risk assessment is not necessary are when immediate management action is preferentially required, well-described data about the risk are available, the case is simple and the risk can be handled sufficiently on the basis of common sense. The cases in which risk assessment is necessary are when there are not enough data on risk and uncertainty of the data is large, a number of assessment potentially clash with one another, the case imposes a considerable burden on risk manager or stakeholders, additional information is necessary to set a direction of management for risk managers, risk baseline estimate is to be made, food-originated hazards cause serious health and trade issues and the country intends to export or import new foods (Table 1_1). Information to be included in risk profile is listed in Fig. 1_1.

<Table 1_1. Criteria for Risk Assessment Necessity>

Cases in which risk assessment may not be necessary	Cases in which risk assessment is necessary
• Immediate handling of problem is necessary. • Risk is well described by confirmed data. • Risk management decision can be made without risk assessment. • Problem is relatively simpler. • Problem is not subject to regulatory concern. • Hazard is not distinguished from natural properties in human body. • Problem can be handled sufficiently based on common sense.	• Data are not sufficient or very uncertain. • A number of values potentially clash with one another. • Regulatory officers or stakeholders have a high level of interest in the issue. • Continuous decision making is required. • Risk manager needs information about guidelines. • Risk manager requires to reference estimates of hazards. • Problem involves a pathogen or a substance that triggers risk swiftly or can result in a serious issue concerning public health or trade conflict. • Domestic standard is stronger than international. • New foods are exported/ imported by country.

Information Included in Risk Profile	
• Summary of food safety issues • Hazards and related foods • Pathway of food contamination by hazards • Possibility of illegal use or misuse • Stakeholders • Information to be checked through risk assessment • Types of hazards and their physical and chemical characteristics • Hazard production/ use • Direct use/ indirect exposure • Characteristics of risk to human body and degree of harmfulness • Large-consumption group, sensitive group • Extensive management targets: Raw materials/ processed items	• Matters to be noted in the stage of food production and distribution • Food intake, hazarod intake • Domestic and international management criteria and operating conditions • Conditions for triggering risk on human body and frequency of risk occurrence • Domestic and international incidents/ accidents • Risk priority • Test method • Insufficient data at the present point in time • Necessity of risk assessment

<Fig. 1_1. Risk Profile >

1-5. Procedures of Risk Assessment on Agricultural, Livestock and Fisheries Products

Risk assessment is carried out through hazard identification, hazard characterization, exposure assessment and risk characterization. Then, impact of the respective agricultural and animal-originated food on human health is examined.

❶ Hazard Identification: Toxicity of chemical hazard is evaluated and hazard to human body is identified.

❷ Hazard Characterization: NOAEL and BMDL are set through dose - response assessment in relation to the risk of chemical hazards. In addition, for quantitative assessment of harmfulness to human body, data uncertainty is evaluated and HBGV is set.

❸Exposure Assessment: Sources of chemical hazard' exposure to human body are identified. In addition, residual amount in foods and intake by human

are evaluated.

❹Risk Characterization: This is a process to set an appropriate management level (MRL) considering the dose of chemical hazards in light of HBGV, to check the margin of safety (MOS) in comparison to NOAEL and to compare margin of exposure (MOE) in comparison to HBGV.

However, in case it is difficult to carry out assessment through all of the procedures above as a result of limitations in science and technology levels and data available at present, some of the procedures can be omitted or a new risk assessment technology can be applied.

2. Risk Assessment for Chemical Hazards in Agricultural and Animal-originated Foods

Chemical hazards in agricultural and animal-originated foods are pesticides, veterinary drugs and environmental contaminants, such as heavy metals, to which food products are exposed during the course of production. In addition, various additives used in food production and processing stages are included. The characteristics of risk by chemical hazard are compared in Table 2_1.

<Table 2_1. Comparison of Risk Characteristics by Chemical Hazard>

Risk Indicator	Veterinary Drug	Agricultural Pesticide	Environmental Contaminants	Food Additives
Chemical Characteristics	Grouped by pharmacological action	Mostly antimicrobial agents, insecticides and herbicides	Heavy metals, POPs and fungal toxins with high level of accumulation in human body	Categorized by use
Risk	Hepatoxicity and nephrotoxicity caused by human intestinal bacterial flora impact to be toxicological endpoints	Nephrotoxicity and reproductive toxicity to be toxicological endpoints	Carcinogenicity, endocrine disruption and reproductive toxicity to be toxicological endpoints	Hepatoxicity, nephrotoxicity and various toxicity to be toxicological endpoints
Exposure Characteristics	Limited to livestock products	In all foods	In all foods	Mainly in processed foods
Risk Management Characteristics	MRL setting	MRL setting	HBGL setting, MOE analysis	Addition standard setting

Divided into qualitative assessment to verify characteristics of risk and quantitative assessment that includes a process to quantify the degree of occurrence possibility of risk, risk assessment is comprised of four stages, which are hazard identification, hazard characterization, exposure assessment and risk characterization. Hazard identification is the first stage of risk assessment. This is to check the risk on human health caused by agricultural and animal-originated chemicals. Hazard identification includes verifying physical and chemical characteristics of hazard, checking toxicokinetics and action of the hazard in human body, conducting toxicological assessment and analyzing the results of human

epidemiological study. In the stage of hazard identification, point of departure (POD) for risk assessment is decided through dose - response evaluation on the basis of assessment data for qualitative and quantitative assessment of hazards. In addition, considering uncertainty of POD, level of risk on human body (or health-based guidance values (HBGV)) is set.

Exposure assessment is to assess the estimated amount of human body exposure based on food intakes by population group. In the stage of risk characterization, margin of exposure (MOE) or margin of safety (MOS) is found through comparative evaluation on the estimated amounts of hazard exposure and HBGVs by population group. Then, an appropriate safety management level or a safety management goal is set and recommended so as to ensure safe and efficient risk management.

2-1. Hazard Identification

This is a process to check toxicity or harmfulness of hazards in human body based on scientific data. Information relating to risk, such as status of use, characteristics of chemical structure, results of toxicity test, target organs and results of epidemiological study, is collected and analyzed, and thus the risk of agricultural and animal-originated hazards is identified.

1) Considerations for Assessment Data

Internationally recognized bio-dynamics data (papers published in scientific journals), clinical trial data and toxicity test data (data prepared in compliance with OECD test guidelines and national test guidelines, data prepared by GLP organization), physical and chemical information and information about impact on environment must be assessed preferentially. Internationally distinguished papers (SCI papers), toxicity information summary or publications by advanced foreign regulatory organizations (WHO IPCS Committee, JECFA, JMPR, IARC, EPA, FDA, NTP and EU), government reports, monographs and recommendations can also be used. While the priority is to be placed on successfully completed bio-dynamics study results, if such results are not available, results of chronic toxicity test or two-year carcinogenicity test conducted on rodents can be used. Latest toxicity test data must be reviewed preferentially.

Period and method of exposure in toxicity test conducted for the purpose of risk

assessment must be similar to exposure periods and pathways for humans. In assessing human response to life-cycle exposure, toxicity test through long-term (2-year) administration on rodents, such as rats and mice, is used. This is because, for rats and mice, the physiological time of two years is equivalent to 70 human years. In addition, information about the occurrence of aging-related diseases (including cancer) without any relevance with toxicity caused by life-cycle exposure and administration of substances can be obtained. For long-term toxicity test with an exception of carcinogenicity test, a toxicity test for 6 - 12 months on rodents is appropriate.

Acute or subacute toxicity data can be used in assessing risk in such situations as high-dose exposure as a result of accidents in worksites or short-term exposure to chemicals in high concentration levels as a result of disasters. In case exposure pattern is repeated in a cycle of five days a week or eight hours a day, results of a repetitive exposure test based on the same exposure cycle are used. As for medium (food or drinking water) used in administration of substances for animal toxicity test, it is advised to use the same medium as in human exposure test.

For principles of dose setting and lab animal selection (test conditions and substance analysis) for toxicity test aimed at hazard identification, guidelines from international organizations and domestic and foreign regulatory organizations can be used for reference. If using toxicity test data to suggest evidences about carcinogenicity, reliability of the data must be examined sufficiently. Positive results consistently reported by successfully implemented studies on bio-dynamics can be the most powerful evidence. If appropriate studies are not available, consistent results of successfully implemented animal test (tumor occurrence dose - dependently increasing in one or more species) can be used as an evidence in determining the status of a substance being carcinogenic. Consistency must be examined in relation to results from observation on experimental animals, results of toxicity tests reported of the target substance and information reported in the past up to the recent time. If it is not acknowledged that a number of similar tests produced consistent results, this means that the test methods and results lack reliability.

Results of metabolic studies, such as studies on toxico-kinetics of substances, and of studies on structure - activity relationship and toxic effects are used as basic data in identifying the degree of toxicity of substances. These data are not directly used in calculating toxicity value (NOAEL (no observed adverse effect level) or LOAEL

(lowest observed adverse effect level)).

In relation to substances that are subject to the risk of exposure to risk - sensitive groups, such as pregnant women and children, the related data must be examined more carefully in the course of hazard identification.

2) Assessment on Substance Characteristics

Biological action is estimated based on characteristics of the target substance by analyzing data on physicochemical structure, molecular weight, powdered form, melting point, boiling point, solubility, accumulative property (Ko/w), volatility, photo - degradability, particle size, chemical characteristics, pharmaco-toxicity, amount of use and status of use of the substance concerned. To preferentially obtain information about physicochemical characteristics and toxicity, web-based databases listed below are mainly used.

- International Programme on Chemical Safety (INCHEM)
- US National Library of Medicine (TOXNET)
- Agency for Toxic Substances and Disease Registry (ATSDR) and
- International Uniform Chemical Information Database (IUCLID)

3) (Chemical) Structure - Activity Relationship (SAR) Assessment

A number of models to estimate the degree of hazard or risk of a substance based on physicochemical characteristics of the substance have been developed and are being applied in risk assessment. These models are collectively referred to as (quantitative) (chemical) structure - activity relationship ((Q) SAR) assessment model.

Toxicity test of compounds is conducted by experienced toxicologists using numerous lab animals in a strictly controlled facility. In case of a chronic toxicity test using rodents, animal administration alone takes approximately two years. Toxicity test on all chemicals, as such, can be a considerable burden both physically and in terms of time. Therefore, predicting toxicity of a chemical through QSAR assessment method holds great significance.

REACH (Registration, Evaluation, Authorization and Restriction of Chemicals), an European chemical evaluation and registration system, acknowledges chemical toxicity prediction data prepared through the verified QSAR. Accordingly, preparing verified QSAR data has surfaced as an important operation. QSAR is a model to predict toxicity and biological characteristics of a substance by comparatively analyzing it against chemical substances of similar types for which the toxicity is already identified on the basis of data on chemical structure and physicochemical characteristics (CAS No., molecular weight, particle size, pKa, melting point, boiling point, solubility, octanol - water partition coefficient (log Po/w) and chemical structure).

OECD introduces the OECD QSAR Application Toolbox (www.oecd.org/env/existingchemicals/qasr) with which to assess impact of chemicals on aquatic environment and to predict bio-degradability, toxicity and ecotoxicity of the chemicals. EPA of the U.S. is implementing such projects as Toxcast in order to predict characteristics and the degree of toxicity using QASR model before proceeding with actual toxicity test. In Europe, together with REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) system implementation, Toxtree program (http://ecb.jrc.ec.europa.eu/qsar/qsar-tools) for QSAR toxicity test is being proposed.

Denmark introduces Danish (Q)SAR database (http://130.226.165.14/index.html) as a QSAR model. In Korea, the Ministry of Environment recognizes QSAR assessment as data for some toxicity (acute and mutagenicity) and biodegradability tests. Of QSAR programs, Toxtree software is an open source program enabling toxicity prediction of compounds using decision tree. When CAS number or structural formula of a chemical is entered, this software analyzes the chemical using Cramer classification and Benigni-Bossa's mutagenicity/ carcinogenicity classification techniques.

4) Toxicokinetic and Pharmacokinetic Assessment

This refers to assessment on absorption, distribution, metabolism, excretion and accumulation of chemicals in human body. In general, chemicals are administered through exposure pathways in experimental animals and are analyzed in relation to

their use, transportation, conversion and excretion in and from the body. Through this process, absorption rate, plasma half life, time to reach maximum concentration in plasma and excretion rate are calculated.

Then, based on distribution amount demarcation in live organs and blood, the degree of risk is quantitatively assessed. Recently, there are movements to minimize toxicity tests using lab animals by replacing them with test tube experiments under 3R principle (refinement, reduction and replacement). However, it is difficult to replace toxicokinetic and pharmacokinetic tests with other experiments, and thus the tests are being conducted entirely dependent on the use of lab animals.

5) Toxicological Endpoint Assessment

Toxicity text data assessment for toxicological endpoint assessment is the most important process in the stage of hazard identification. This is to assess oral toxicity, dermal toxicity and inhalation toxicity according to exposure pathways of chemicals. As for ordinary toxicity, it is to assess overall impact of the toxic substance on biologic system. Toxicity is divided into acute or single-dose toxicity, subacute or short-term toxicity and chronic or long-term toxicity according to administration count and period.

For special toxicity, this is a process to assess impact on special functions of biologic system or organ functions. Special toxicity is categorized into genetic toxicity, carcinogenicity, reproductive toxicity, endocrine disruption, hepatotoxicity, renal toxicity, neurotoxicity or chemical dependency, immunotoxicity, pulmonary toxicity, local toxicity and epispasticity. In addition, although not direct impact on living body, impact on normal germs in human body that play an extremely important role in maintaining health while keeping a symbiotic relationship with human body is assessed as an indirect assessment of impact on human health (See Attachment VI.).

❶ Acute Toxicity Test

Both female and male rodents or non-rodent animals of two species or more are used. Chemicals are administered once orally. The intensity of toxicity is estimated by calculating 50% fatal dose (LD50) (Relative Non-toxicity: >5,000; Weak Toxicity: 500-5,000; Medium Toxicity: 50-500; High Toxicity: <50 mg/kg bw)

❷ Short-term Toxicity Test

Both female and male rodents or non-rodent animals of two species or more are used. Chemicals are administered orally every day for three weeks - six months. During the period of administration, the animals' general conditions and weight, feed and sample intake amount and amount of water drinking are observed. In addition, urine test, ophthalmologic test, visual check of the animals' organ tissues, histopathologic test and hematologic and blood biochemical test are conducted. At the same time, residual amounts of samples/ metabolites in muscle, fat, liver and kidney are measured. The most acute toxicity is identified and LOAEL and NOAEL are calculated.

❸ Chronic Toxicity Test

Both female and male lab animals of one or more species are used. Chemicals are administered daily over six months - life cycle of the animal (depending on animal's lifespan). During the period of administration, animals' general conditions, weight, feed and sample intake amount and amount of water drinking are observe. In addition, urine test, ophthalmologic test, visual check of the animals' organ tissues, histopathologic test and hematologic and blood biochemical test (plasma biochemical test) are conducted.

LOAEL and NOAEL are calculated for each of the recognized toxicities.

❹ Reproductive Toxicity Test

This test is about impact on overall reproduction process of animals, such as the impact on animals' reproductive capacity and posterity of the animals. Basically, a teratogenicity test and a first-generation reproductive toxicity test are included. In some cases, multi-generation reproductive toxicity test and endocrine disruption test are conducted. For teratogenicity test, it is advisable to select species subject to a low level of teratogenesis occurrence. In principle, administration is carried out daily during the organogenic period of fetus (day 6 - 15 of pregnancy for rats). Reproductive toxicity test is conducted when found necessary based on the results of teratogenicity test or when impact is suspected on reproduction, such as reproductive capacity and partus of male and female animals, based on separately available knowledge. Reproduction process from pre-pregnancy to weaning period is divided into pre-pregnancy, early pregnancy, perinatal and lactating periods so as to accurately identify impact on gametogenesis. The tested chemical is identified of its status of being a reproductively toxic substance and LOAEL and NOAEL are calculated for each of the recognized toxicities.

❺ Genotoxicity Test

This is a test to check genetic variation caused by chemicals. Genotoxicity test is divided into unscheduled DNA synthesis test to check DNA damages, reverse mutation test using bacteria with genetic mutation induction as an indicator, in vitro chromosomal abnormality test using cultured mammalian cells with chromosomal abnormality induction as an indicator, in vivo micronucleus test using rodent hemoblast and dominant lethal test on rodents. In addition, when recognized necessary based on results of the tests above, other toxicity tests and tests concerning pharmacological action, it is advised to conduct addition genotoxicity tests. The target chemical is identified of its status of being positive or negative to genotoxicity based on the test results.

❻ Carcinogenicity Test

This test is conducted on already known carcinogenic substances or substances suspected of carcinogenicity and also on chemicals with similar chemical structures or pharmacological actions, found to be positive in short-term carcinogenicity test, such as genotoxicity test, or suspected of carcinogenicity as a result of toxicity test.

To male and female animals of two species or more, the target substance is administered orally every day for 18 - 24 months or longer and the occurrence of cancer (malignant tumor) is observed both qualitatively and quantitatively. During the period of administration, the animals' general conditions and weight are observed. Upon completion of test, the animals' organs and tissues are visually checked and a histopathologic test is conducted to identify the occurrence of tumorous lesion. If necessary, red and white blood cell counts are measured through peripheral blood collection and smear test is conducted. Carcinogenicity is identified and LOAEL and NOAEL is set for each of the recognized toxicities.

❼ Test for Impact on Normal Bacterial Flora in Intestine

This test is to check impact of antibiotic and antibacterial substances in foods on normal bacterial flora in human intestine. In case the target substance has microbial effects and flows into human colon and displays the effects or if the related information does not exist, a test on disruption of defence wall against bacterial flora in intestinal mucosa, tolerance induction test or metabolic abnormality test with microbial toxicity as an indicator in a test tube or live body is conducted. As for the test on disruption of defence wall against bacterial flora in intestinal mucosa, minimum inhibitory concentration test using representative bacillus of normal bacterial

flora in human intestine (minimum 100 strains of 10 species) originated from human excrements is conducted. Other tests include a test on anaerobic flow culture system for normal bacterial flora in intestine and a test using mice for normal bacterial flora expression in human intestine. Based on the results of tests, the most acute normal bacterial flora toxicity is identified and NOAEC is calculated.

❽ Immunotoxicity Test

Necessity of this test is determined according to the usage, formulation and chemical characteristics of the target substance. In case abnormality in immune reaction is suspected as a result of subacute and chronic toxicity tests or in case the substance can act as an antigen in living body, impact of the substance on immune system is examined. This test is divided into immunotoxicity, antigenicity and skin sensitization tests. As for skin sensitization test, it is further divided into a test using guinea pigs, local lymph node proliferation test using mice and other skin sensitization tests. This is test to assess impact of chemical on immune system. For this, immunity improvement or reduction is observed. Abnormalities in immune system are identified and LOAEL and NOAEL are set by each of the recognized toxicities.

❾ Other Special Toxicity Tests

The necessity of these tests are determined according to the usage, formulation, chemical characteristics and action of the target substance. Other special toxicity tests include neurotoxicity, local stimulation, hematotoxicity, hepatotoxicity and renal toxicity tests.

6) Bio-dynamics Data Assessment

Based on bio-dynamics data, impact of the exposure to chemicals on human health is directly identified and the levels of risk to health according to the degrees of exposure can be compared. The data of a well planned and successfully implemented bio-dynamics study are the most powerful evidence. However, they are subject to qualitative and quantitative limitations. Therefore, a number of variables must be taken into consideration in terms of data accuracy and reliability. The most frequently used methods of bio-dynamics studies are as listed below. Appropriate data for each risk occurrence situation must be selected.

❶ Cohort Studies (CS)

This is a method to select a specific population group and to trace occurrence of impacts harmful to health with the group. CS is divided into prospective CS to identify impact in the future from the time of exposure at present and retrospective CS to study the impact from the time of exposure in the past. CS enables a relatively accurate identification of relevance between exposure information and cause. On the other hand, it requires large amounts of cost, labor and time. In addition, there is a possibility of target omission if study target is traced (prospective CS) over a long period of time.

❷ Case - Control Studies

This is a method to verify and compare relevance between the impact of exposure to target substance and risk to health by selecting a person who has disease and a person as a control from the same group. This is useful in the study of dynamics about rare diseases or diseases with long latent periods. On the other hand, it is associated with a problem in terms of accuracy and reliability when collecting information about the factors of exposure in the past. It may also be difficult to select an appropriate control group for the patient group.

❸ Cross-sectional Studies

This is a method to concurrently collect data on exposure and disease, and thus to verify relevance between the exposure and disease incidence.
An advantage of cross-section study is that it is convenient to directly measure current exposure, and thus to conduct the study. However, as a weakness, causality of the two factors cannot be identified clearly as exposure and disease are concurrently measured.
In addition, as disease status can bring changes to exposure pattern, it is unable to obtain sufficient samples for diseases of which the level of incidence is low.

2-2. Hazard Characterization

Hazard characterization is a stage to calculate LOAEL, NOAEL and benchmark dose level (BMDL) of hazard by qualitatively or quantitatively assessing impact of the hazard on human health through does - response assessment and to set acceptable daily intake (ADI), tolerable daily intake (TDI) and acute reference dose (ARfD) of

the hazard. According to toxicological characteristics of a hazard, the assessment method is divided into toxicological threshold approach and non-threshold effect evaluation. An appropriate approach must be used for each hazard.

In case a chemical is found positive for genotoxicity, produced results to be classified as positive in chronic toxicity or carcinogenicity test using lab animals and has been identified of carcinogenesis in human body, non-threshold effect evaluation technique must be used of which toxicological thresholds cannot be decided.

However, other chemicals are non-carcinogenic, and thus their toxicological thresholds can be decided. Therefore, for these chemicals, risk assessment is carried out using an appropriate approach.

1) Toxicological Threshold Approach

Toxicological endpoint is checked based on the results of a strictly conducted bio-dynamics test or of a toxicity test, and thus LOAEL, NOAEL and BMDL, the points of departure (POD) for setting ADI, TDI and ARfD, are set.

❶ NOAEL and LOAEL

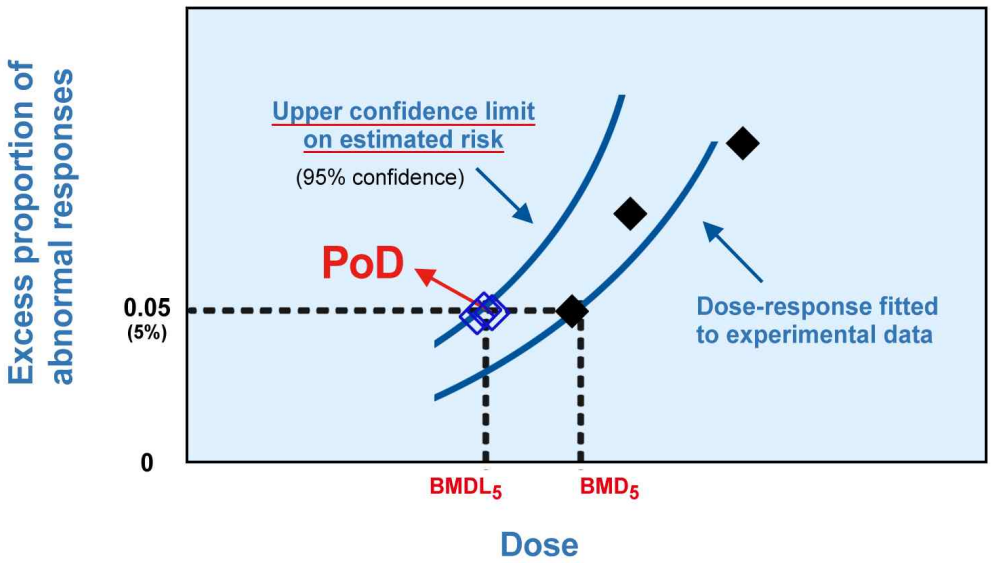
NOAEL, the maximum dose of which toxicity or side effect caused by administration of hazard in toxicity test using test tubes or animal test does not produce statistically or biologically significant differences from control group, and LOAEL, the minimum dose of which toxicity or side effect produces statically or biological significant differences from control group, are set. These doses are selected from those announced by test. Therefore, it is advisable for the dose group to have capacity of 3 or more with an appropriate common ratio (2 - 5).

❷ BMDL

BMDL refers to a dose within a confidence level (90 - 95% mainly used) that does not display significant differences from control group on dose - response curve. BMDL approach can be applied to both risk prediction assessment on sensitive group and assessment of non-carcinogenic substances. Dose - response relationship is more sufficiently considered and statistical analysis is strengthened than the existing NOAEL or LOAEL approach. Enabling more multifaceted assessment as such, this analysis technique is widely used as of late. First introduced by Kenneth Crump

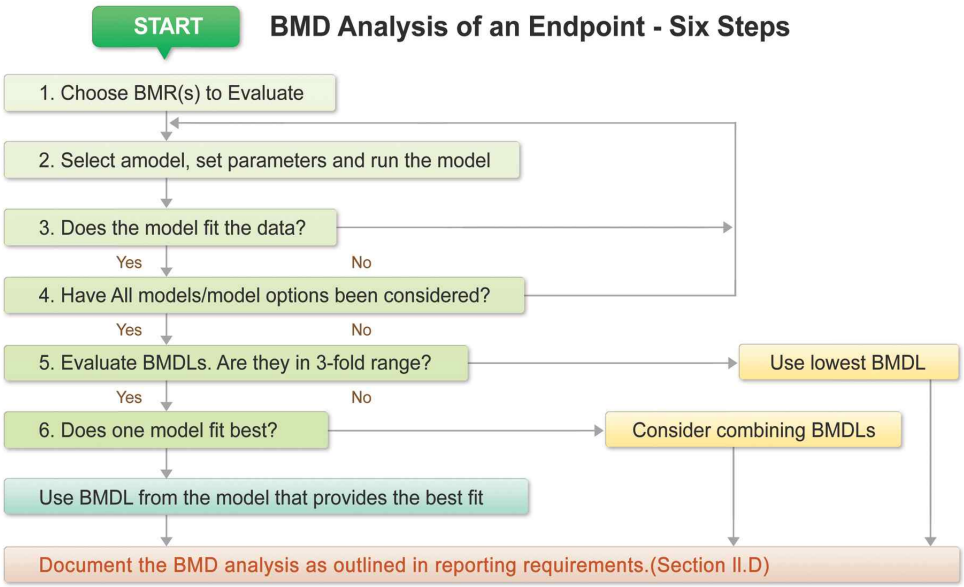
(1984), BMD was spread wide at a forum on risk assessment in relation to BMD held by EPA of the U.S.

In 2000, EPA developed Benchmark Dose Software together with descriptive guidelines on BMD and has since been distributing the software. The use of BMDL assessment is recommended in a case where, although the substance is not completely carcinogenic, data for NOAEL are insufficient, or when statistical consideration on dose - response is necessary. For BMDL assessment, Benchmark Dose Software (BMDS v. 2.0, http://www.epa. gov/NCEA/bmds) is being provided at the moment.



<Fig. 2_1. BMD and BMDL Setting on Dose - Response Curve>

BMDL analysis is carried out in six stages as suggested in Fig. 2_2.



<Fig. 2_2. Benchmark Dose Level (BMDL) Analysis Procedures>

The six-stage procedures are as follows:
First, select a benchmark response to assess. Second, select an appropriate model and an indicator and start the model. Third, check if the model matches well with actual data. Fourth, check if all available models have been sufficiently taken into consideration. Fifth, assess BMDL and check if it is within three times of BMD. Sixth, check the most suitable model and set BMDL.

<Example of BMDL Assessment>

▪ Lab Animal: Mice (150) ▪ Toxicological Endpoint: Hepatic cancer ▪ Data on hepatic cancer incidence by dose

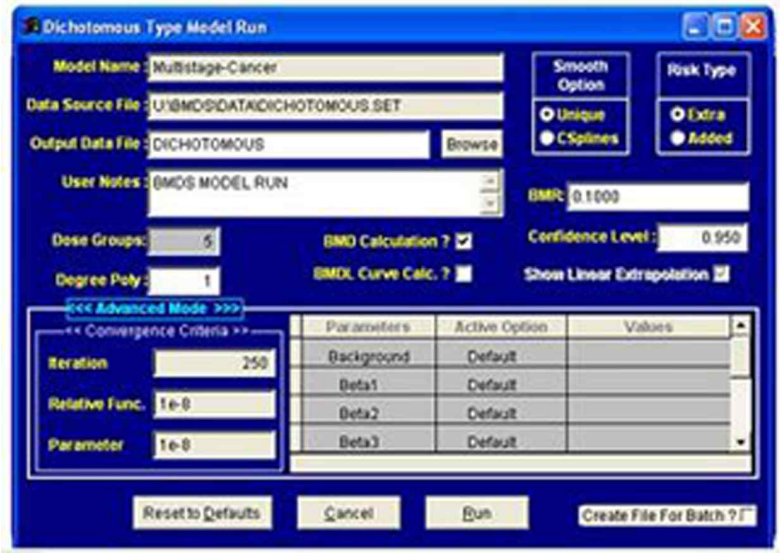
Dose (㎎/㎏ bw/day)	No. of Animals	No. of Animals with Hepatic Cancer
0	100	0
50	100	5
100	100	30
150	100	65
200	100	68

• Select an appropriate model.

As the selected data are about hepatic cancer lesion, select multistage-cancer of dichotomous data.

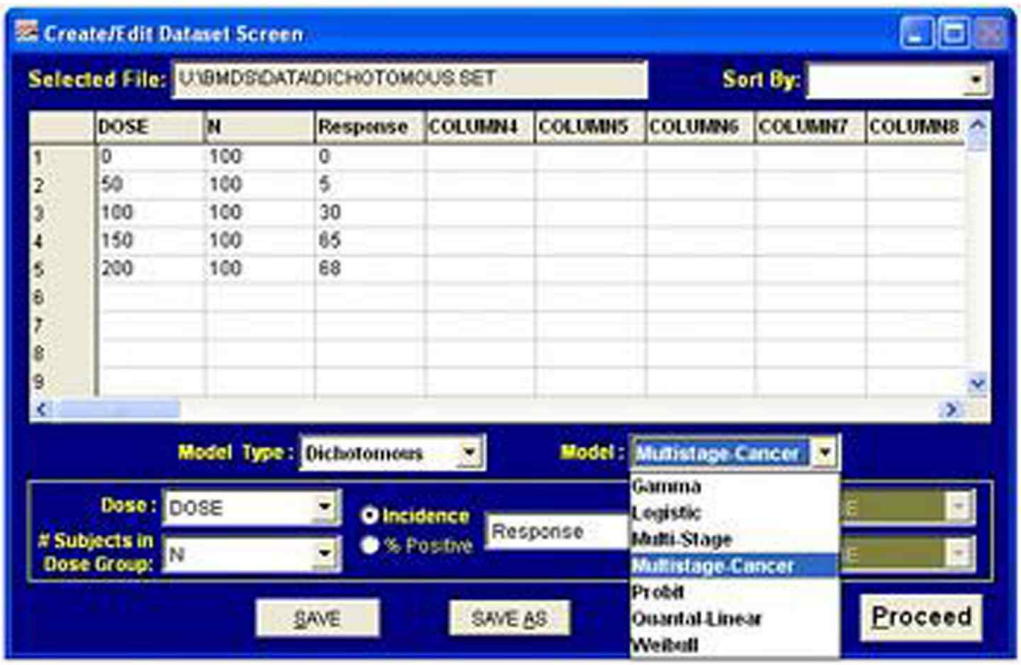
- Enter data to and start BMD software.
- Derive BMD, BMDL and CSF (Cancer Slope Factor, BMR/BMDL).

Multistage-Cancer Model: Parameter Setting

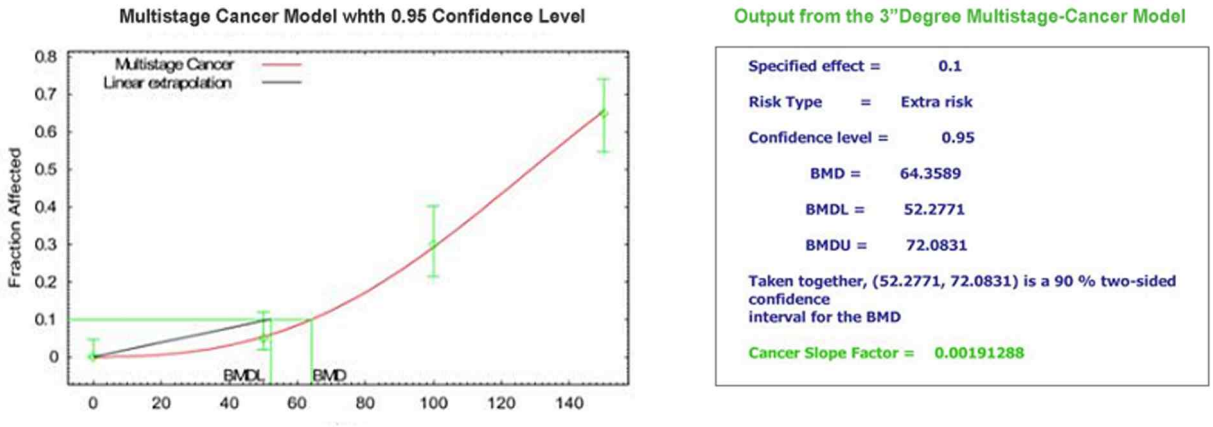


<Fig. 2_3. Model Setting>

Multistage-Cancer Model - Create/Edit Dataset Screen



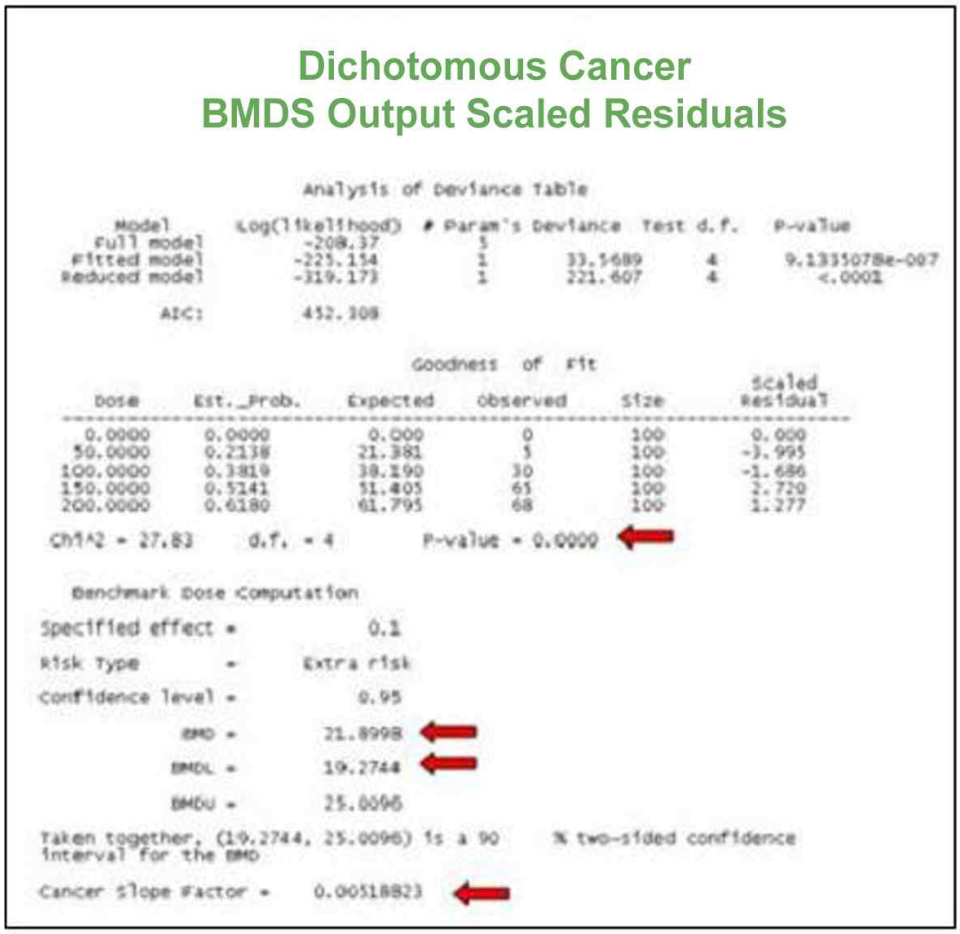
<Fig. 2_4. Data Input>



<Fig. 2_5. Checking Fitting on Dose - Response Curve>

▪ Verify the result.

Check P value (>0.1) and AIC value (lower values are more accurate) and verify appropriateness of model and fitting method.



<Fig. 2_6. Calculating BMD, BMDL and CL Factor>

▪ Verify result.

In mice, BMDL for hepatic cancer incidence is 19.2744 mg/kg bw/day (Confidence Level: 95%).

❸ Uncertainty Factor (UF) Setting and Application

There are factors to be taken into consideration to directly derive risks for human based on animal test data. The examples include differences between animal species and between individuals. Therefore, to secure sufficient safety for extrapolation, UF (10 - 1000) is applied to calibrate uncertainties, such as differences between species and individuals.

▪ Toxico-dynamic and toxico-kinetic differences exist between human and lab animals. based on physiological data by animal, UF of 10 is mainly applied.

▪ After calibration of interspecific differences from animal to human, UF of 10 is applied to toxico-dynamically and toxico-kinetically calibrate differences in sensitivity within human group.

▪ In case chronic toxicity test results are not available or data on toxicity test are insufficient, and thus sub-chronic toxicity test results are to be used for ADI setting, it will be necessary to additionally apply UF between 1 and 10 according to the test.

< Table 2_2. Uncertainty Factors Mainly Used in Risk Assessment>

Category	UF (Default Value)
Differences between Animal Species - Mice - Rats - Rabbits - Dogs	10 (4×2.5) Toxicokinetic Uncertainty (TK) × Toxicodynamic Uncertainty (TD)
Differences between Individuals	10 (3.2×3.2, TK×TD)
Differences in Exposure Time and Exposure Pathway - Chronic ➡ Chronic - Subacute ➡ Sub-chronic - Sub-chronic ➡ Chronic - Other	1 10 10 1 ~ 10
Characteristics of Toxicity Impact	1 ~ 10
Dose - Response Curve	1
Data Reliability	1 ~ 10
LOAEL ➡ NOAEL	10

- When ADI is calculated based on LOAEL as NOAEL cannot be set in chronic toxicity test, a UF between 1 and 10 is additionally applied or BMDL is set.
- In case NOAEL is used or test data are found insufficient, a UF between 1 and 3 can be additionally applied.
- Additional UFs can be applied considering various elements, such as irreversibility of toxicity effect, effects associated with age or population group (enzymatic system underdevelopment, difference in microbial flora in intestine, difference in metabolic ability and difference by exposure age) and carcinogenic mechanism.

❹ Health-based Guidance Level (HBGL)

HBGL refers to a daily exposure per kg of body weight (mg/kg b.w/ both weight) at which no hazardous impacts are generated even when human body is exposed to the hazard throughout the life cycle. HBGL includes ADI, TDI and ARfD. ADI is applied to substances subject to permit (food additives, pesticides and veterinary drugs) that are used intentionally. TDI is applied to substances to which human body

is unintentionally exposed through the environment. ARfD is used as HBGL for substances that have low accumulative toxicity and causes most acute impact through temporary exposure (Ex.: Organophosphates and clenbuterol).

2) Non-threshold Effect Evaluation

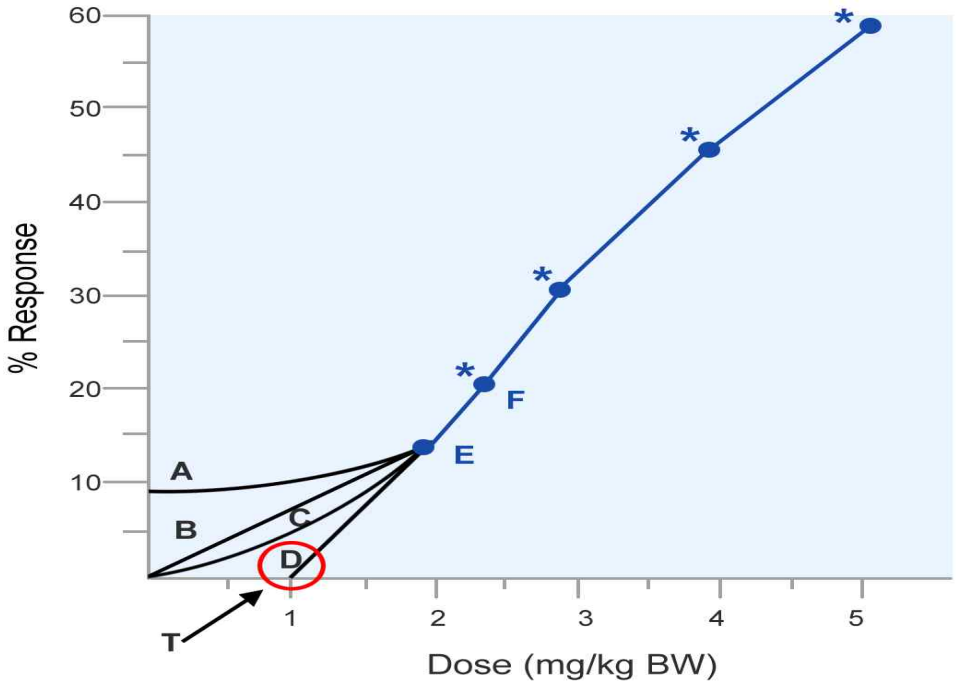
Substances that are positive for genotoxicity in test tube or living body and, at the same time, produce cell proliferation, such as tumor formation, are categorized as genotoxic carcinogens. Even a trace amount of these substances can cause gene damage, and thus lead to carcinogenesis. Therefore, there threshold cannot be decided.

Accordingly, NOAEL and HBGL settings are disabled and this technique is not authorized of use on substances that are subject to permit. In addition, the recent trend is that food safety management is carried out in ALARA (as low as reasonably achievable) level. ALARA is a type of risk management option. As management is generally carried out in the level of quantitative limit of test method, trace amount requires a ultra precision test method. Therefore, economic value needs to be taken into consideration.

Bio-dynamics data are used very importantly as a basis for judging threshold/ non-threshold level. In other words, bio-dynamics data are clinical data used in assessing whether or not exposure dose triggers carcinogenesis in human during the exposure period. However, bio-dynamics data are subject to such issues as low effectiveness and unavailability. There are also limited in many cases. Therefore, a scientific and systematic analysis is required. In many cases, substances categorized as Group 1A (carcinogenic to humans), Group 2A (probably carcinogenic to humans) and Group 2B (possibly carcinogenic to humans) by International Agency for Research on Cancer (IARC) have not been identified of their carcinogenic effects through tests conducted so far. Therefore, it is necessary to closely analyze genotoxicity data and results of carcinogenicity evaluation in lab animals.

When threshold evaluation is difficult, the previously described BMDL assessment on dose - response curve can be conducted. Linear extrapolation technique can also be used. This is a method to estimate reactive dose through linear extrapolation at a point where response has been confirmed in order to set LOAEL.

<Fig. 2_7> is a response curve. Although a number of dose - response curves, such as from A to D, can be estimated, in linear extrapolation approach, linear extrapolation is carried out with an inclination of F - E on dose - response curve and a point where the value is 0 is set as the LOAEL.



<Fig. 2_7. Linear Extrapolation, Evaluation with Dose D as Threshold>

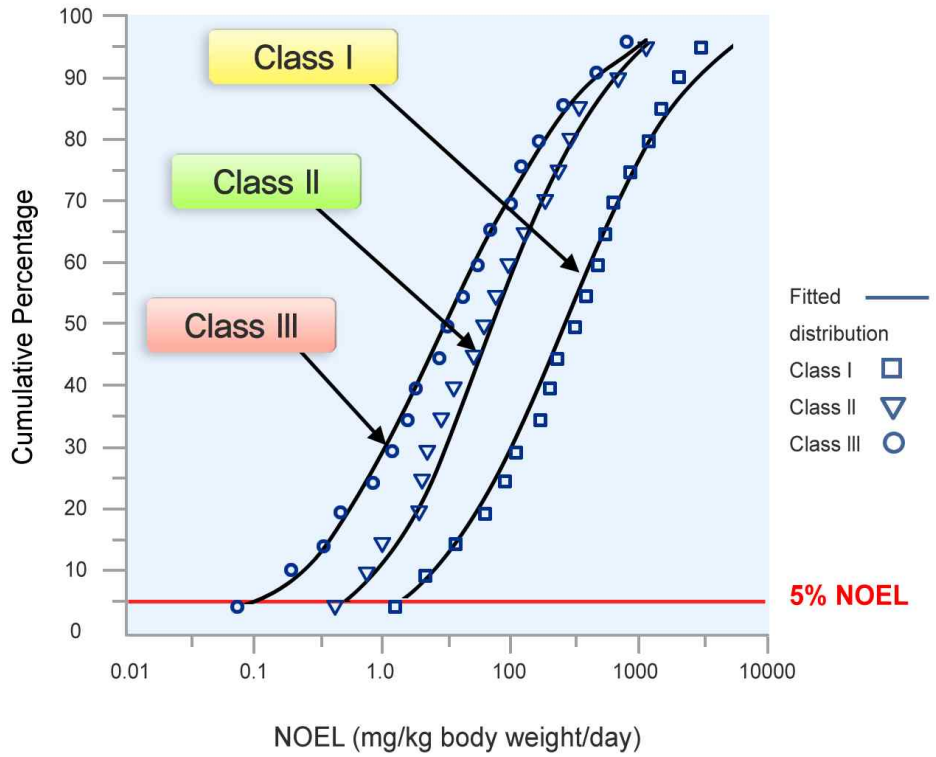
3) Threshold of Toxicological Concern (TTC) Assessment

TTC approach is a practical risk assessment technique in setting human exposure threshold and appropriate management level for almost all chemicals. Chemical risk assessment requires numerous data, such as toxicity test data and physical/ chemical information.

Even such information is insufficient, TTC approach can be used to estimate approximate toxicity level based on dose - response information and chemical structure information about chemicals of the similar system. As such, this is a preliminary risk assessment technique for target substances. Based on the results of preliminary risk assessment, toxicological threshold is estimated and preferential management criteria are set. Then, necessity of additional toxicity test is determined.

❶ TTC Evaluation of Non-carcinogens

TTC assessment on non-carcinogens was first proposed by Cramer et al. (1978). Since then, it has been supplemented by Munro et al. (1996) and Kroes et al. (2004). Using this method, 613 of already known non-carcinogens are categorized into classes I - III according to their chemical structures and toxicity characteristics. Then, dose - response curves are drawn up for these substances and 5% non-toxic dose level (NOEL) is set as a toxicological threshold.



<Fig. 2_8. NOEL Plot of Chemicals (613) on Dose - Response Curve>

<Table 2_3. NOAEL and Exposure Threshold of Chemicals Classified with TTC>

Classification	Structure Classes for Chemicals	5% NOAEL (mg/kgbw/day)	Exposure Threshold* (mg/person/day)
Class I	Low-toxicity compound of simple structure	3.0	1.8
Class II	Intermediate-level structure compound with toxicity higher than of Class	0.91	0.54
Class III	Composite structure compound metabolized as toxic substance	0.15	0.09

*: Uncertainty Factor: 100, Weight: 60kg applied (Cramer et al., 1978)

❷ TTC Assessment of Carcinogens

TTC assessment on carcinogens was proposed by Munro (1990) and Cheeseman et al. (1999). Based on the intensity of carcinogenicity in lab animals obtained through chronic carcinogenicity test through oral administration of 709 chemicals to rodents (median toxic dose, Log TD50 (toxic dose 50%)), extrapolation is carried out within a range not exerting carcinogenic risk to human body (1/1,000,000 of TD50), and thus human safety dose is estimated.

- Evidentiary Data for Carcinogenic Substances: Intensity of carcinogenicity obtained from the results of chronic carcinogenicity test through oral administration of 709 substances to rodents

- Human Safety Dose: 0.5 ppb (0.5 μg/kg of food) ⇒ 1.5 μg/ person/ day (Assumption: An adult with weight of 60kg takes 1.5kg of solid foods and 1.5kg of water daily.)

- Maximum estimated dose not causing significant risk to human health
  - Non-genotoxic Carcinogen: 1.5 μg/ day/ person; Genotoxic Carcinogen: 0.15 μg/ person/ day (safety factor 10 additionally applied)

<Table 2_4. Thresholds of Carcinogens and Non-carcinogens Using TTC>

Category		**Maximum Estimate Intake without Health Risk (TTC)**
Genotoxic Carcinogens		0.15 ㎍ person/day
Non-genotoxic Carcinogen		1.5 ㎍ person/day
Organophosphates		18 ㎍ person/day
Other Chemicals	Cramer Classes III (Compound structure substance metabolized as toxic substance)	90 ㎍ person/day
	Cramer Classes II (Intermediate structure substance causing significant toxicity)	540 ㎍ person/day
	Cramer Classes I (Simple structure substance metabolized as low toxicity substance)	1,800 ㎍ person/day

2-3. Exposure Assessment

Exposure assessment is a process to estimate human exposure level based on qualitative and (or) qualitative analysis data (food intake, weight by physiological stage, average life expectancy, exposure frequency and estimated exposure amount) of hazards taken through agricultural and animal-originated foods. First, an exposure scenario about a situation relating to exposure occurrence is assumed.

Then, human exposure amount is calculated by investigating exposure pathway, characteristics of the exposed population group and all variables relating to human body exposure. In this chapter, Data to review for exposure assessment are suggested together with classification of Korean population groups by age, average weight by age and food intakes by Korean people. In addition, a method to set the amount of exposure through daily intake is described.

1) Setting Exposure Scenario

As for exposure of harmful chemicals contained in animal-originated foods to human body, four scenarios can be established.

These are exposure through all food groups or by detailed food item, exposure to specific age group, such as children, exposure to obesity group or group with extremely large amount of intake and exposure when there is no information available about food intake.

❶ Scenario of exposure through all food groups or by detailed food item

This scenario is mainly used to assess human exposure of chemicals contained in all animal-originated food groups or food items. It targets adults and uses average weight and average age of the adults as well as average intake of each food item.

❷ Scenario of exposure to specific age group

This scenario can be used in assessing human exposure of harmful chemicals that are especially hazardous to infants and toddlers, such as melamine. To this scenario, average weight and average intake of specific age group (infants or toddlers) must be applied.

❸ Scenario of exposure to obesity group or group with extremely large amount of intake for specific foods

Exposure assessment for a case of large intake is required when toxicity of the respective chemicals is strong. In this case, human exposure assessment is carried out using data on the top 95th percentile intake.

❹ Scenario without any information

In case exposure from food is identified, but the respective food item name is unclear and data on intake, etc. are not available, exposure assessment is carried out assuming that daily intake of an ordinary adult (Body Weight: 60kg) is 3kg (1.5kg of solid food and 1.5kg of liquid).

2) Data for Exposure Assessment

❶ Information about Substance: Molecular formula, structural formula, molecular weight, shape of substance, physical condition, purity, melting point, boiling point, vapor pressure, octanol - water partition coefficient and solubility

❷ Production or import amount

❸ Type of use, classification by use

❹ Form of existence in environment and environmental sustainability

Stability, monitoring data, distribution in environment, degradability in actual use, biodegradability, BOD5, COD or BOD5/COD ratio and degree of accumulation in body are included.

❺ Level of inflow to human body

Human exposure pathway, average food intake, average weight, analysis technique and level of contamination in foods are included.

❻ Other

Studies conducted abroad and management criteria used in foreign countries

3) Basic Data for Exposure Assessment

❶ Korean Population Group Classification and Average Weight

Population groups are classified through the selection of such conditions as physiological growth and development stages, nutrient intake standards and amount of activity based on the data of recommended dietary allowances for Koreans, Korea national health and nutrition examination survey, US EPA/ Exposure Factor Handbook and US EPA/ Early-life Exposure to Carcinogen. The average weight of Korean adults (20 - 64 years of age) is 55kg and the top 95th percentile weight is 77kg.

At present, 55kg is used as the average weight of Korean people in risk assessment. This was calculated by multiplying the rates of each population age group with average weight of the respective age group and adding up the values. The 95th percentile national average weight is 75kg.

<Table 2_5. Korean Population Groups and Average Weight by Age>

Classification	Group	Age	Average Weight (kg)			95th Percentile Weight (kg)		
			Male	Female	Total	Male	Female	Total
Children	Infants	Less than 1	8	7	7.5	9	9	9
	Toddlers	1-2	13	11	12	15	15	15
		3-5	18	16	17	21	22	21.5
	Children	6-11	30	29	29.5	43	41	42
	Juveniles	12-18	44	50	47	78	67	73
Adults		19-64	70	58	64	90	75	83
Elders		65 or older	64	55	60	80	70	75
Average Weight of Korean People		All ages	57	53	55	83	70	77

<Source: Korea National Health and Nutrition Examination Survey (2012), Children and Youth Growth Table (2007)>

❷ Setting Average Life Expectancy of Korean People

The average life expectancy of Korean people is 80 years of age. By gender, the average life expectancy of male and female has been reported as 76 and 83 respectively. Although life expectancy is displaying a trend of increase each year, the average life of Korean people in risk assessment is set as 70 years. For reference, EPA of the U.S. sets estimated life expectancy as 70 years of age for risk assessment (actual average life expectancy of U.S. population groups is 75). In addition, WHO applies 80 years of age.

❸ Physiological Characteristics by Age Group

It must be possible to apply risk assessment to all population groups. In addition, additional consideration must be given to specially sensitive population groups and risk assessment results applicable to these groups must be derived. Results of general risk assessments are applicable to ordinary adults. Population groups for special consideration include infants, children, elders, pregnant women and persons with diabetes or cardiovascular diseases. In particular, pregnant women are characterized with their immunity decreasing considerably during the earlier phase of pregnancy or after giving birth.

During the early phase of pregnancy (6 - 12 weeks), immune cells decrease rapidly and, as a result, immunity is lowered by more than half of non-pregnant women. Therefore, careful attention is necessary to prevent infectious diseases, such as cold. Immune cells (T cell and B cell) decrease sharply during 6 - 12 weeks of pregnancy. From the 13th week, the number of immune cells fall below half of non-pregnant women.

As for persons with cardiovascular diseases, they are a group of people suffering from cardiovascular diseases who have high plasma LDL - cholesterol levels and are confirmed of metabolic syndrome. Therefore, for this population group, risk assessment on organophospates or beta adrenergic agonist type substances must be conducted specially.

Elders have the following characteristics. ① They are often categorized as obese as their body fat rates are high. ② There immunological functions are lowered. Plasma concentration and production of pro-inflammatory cytokine increase and an imbalance occurs in inflammatory response regulation. ③ LDL cholesterol in plasma becomes oxidized and the oxides build up on arterial subcutaneous tissues. As a result, various inflammatory responses increase.

Checking population groups sensitive to specific chemical hazards is important in preparing appropriate safety management plans and risk assessment for these groups.

Population groups sensitive to hazards in foods can vary by characteristics of hazard and toxicity. To verify sensitive groups by hazard, sensitivity markers are set and, through observation of changes in these markers following exposure to chemicals, population groups most acutely affected by the exposure are set. Bio-sensitivity markers are associated with diseases or health risks that occur when human body is exposed to hazards. These markers include the hazard itself, metabolites and substances generated through response to specific cells or molecules. Bio-markers are divided into three types, exposure bio-markers, risk impact bio-markers and sensitivity bio-markers.

▪Exposure Bio-marker: This marker reflects both external and internal exposures to specific hazards in the past and at present. Exposure bio-marker is used in forecasting in internal exposure amount in the future.

▪Risk Impact Bio-marker: This marker reflects biochemical changes caused by toxicity of hazard. Ideal risk impact bio-markers are those reflecting initial changes inside the body caused by exposure before irreversible impact of risk on health appears.

▪Sensitivity Bio-marker: This marker is used in distinguishing individuals that are sensitive to specific hazards. An example is genetic polymorphism, which is to decide phenotype that plays a part in metabolism of hazards.

<Table 2_6. Physiological Characteristics by Age Group>

Classification	Group	Age	Physiological Characteristics
Children	Infants	Less than 1	• This is an important period during which the foundation for human development is established. Rapid growth takes place in various areas of development. • Antibodies obtained from the mother prior to birth start to decrease gradually after birth. They almost completely disappear at around nine months after birth. • As a whole, immune system is immature, and thus infants respond to external hazards sensitively.
	Toddlers	1 - 5	• This is a period in which growth and physical development take place most rapidly. Changes in nervous system (sympathetic and parasympathetic) are prominent. • This is a period in which children are sensitive to neurotoxic substances.
	Children	6 - 11	• This is a period in which physical growth and development take place stably. • Respiratory diseases are most frequently observed. They occur six - seven times a year.
	Juveniles	12 - 18	• The definitions of juvenile by U.S., WHO and FAO are people aged between 15 and 24, between 10 and 19 and between 10 and 24 respectively. • In Korea, juveniles of all ages distinctly display insufficiency of calcium and iron intakes. The problem is particularly serious in female juveniles. • As for calcium, iron and vitamin A, the intake is less than 75% of the recommended level in many cases. As for calcium, 60 - 80% of juveniles do not take it sufficiently. In case of iron, intake insufficiency is observed in female juveniles of all ages and male juveniles aged between 13 and 19.
Adults		19 - 64	• This is a period in which almost no changes are observed unlike of infants, toddlers, children, juveniles and elders. • Lean body mass (LBM) decreases and energy requirement reduces.
Elders		65 or older	• In general, physiological and physical functions deteriorate and psychological changes occur. As a result, self-sustenance and social functions weaken. • Panatrophy and pigmentation occur. In addition, blood vessel elasticity, circulatory function, respiratory function, digestive function, endocrine function, nervous function and sensory function weaken.

❹ Food Intake by Korean People

Basic data on national food intake are food balance sheet and national health and nutrition examination survey results. Food balance sheet is a basic data provided by the Ministry of Agriculture, Food and Rural Affairs. It suggests the amount of food supply as total amount and amount per person per day. National health and nutrition examination survey is conducted by the Ministry of Health and Welfare. This survey is conducted as part of national nutrition survey to investigate food and nutrient intake status, dietary behaviors and food intake frequencies.

To establish exposure scenario for risk assessment on chemicals through the intake of various foods and to conduct exposure assessment in relation to specific age groups, it is very important to accurately understand food intake per person per day by age group.

Food intake analysis table compiled by region on the basis of GEMS/ FOOD (FAO, 2004) data shows food intake status in the Far East region, which is close to Korea.

<Table 2_7. Intake of Key Foods by Region >

(Unit: g/person/day (%))

Food		Middle East (%)	Far East (%)	Africa (%)	South America (%)	North America (%)	Europe (%)
Cereals		140.6 (30.9)	141.5 (27.3)	125.8 (28.8)	105.9 (19.7)	88.1 (12.6)	110.3 (16.5)
Root and Tuber Crops		19.6 (4.3)	38.1 (7.4)	103.9 (23.8)	44.7 (8.3)	59.2 (8.5)	84.3 (12.6)
Sugars		28.4 (6.3)	19.4 (3.7)	20.3 (4.7)	44.7 (8.3)	65.1 (9.3)	36.7 (5.5)
Beans and Vegetables		103.8 (22.8)	149.2 (28.8)	66.8 (15.3)	65.2 (12.1)	124.6 (17.8)	123.4 (18.5)
Nuts and Oils		2.9 (0.6)	5.6 (1.1)	2.8 (0.6)	6.9 (1.3)	3.4 (0.5)	2.6 (0.4)
Fruits		57.7 (12.7)	53.6 (10.4)	50.0 (11.5)	97.4 (18.1)	71.5 (10.2)	72.8 (10.9)
Meats and Entrails		33.7 (7.4)	29.5 (5.7)	17.2 (3.9)	63.4 (11.8)	100.4 (14.4)	65.2 (9.7)
Eggs	Egg	4.7 (1.0)	8.6 (1.7)	2.2 (0.5)	9.5 (1.8)	13.9 (2.0)	12.1 (1.8)
Milk		42.5 (9.4)	44.5 (8.6)	30.5 (7.0)	76.8 (14.3)	123.6 (17.7)	119.7 (17.9)
Dairy Products		14.9 (3.3)	11.0 (2.1)	9.6 (2.2)	15.9 (3.0)	35.1 (5.0)	27.7 (4.1)
Fish	Seawater	0.5 (0.1)	4.4 (0.8)	0.6 (0.1)	1.4 (0.3)	1.5 (0.2)	1.2 (0.2)
	Freshwater	1.0 (0.2)	7.1 (1.4)	2.2 (0.5)	1.5 (0.3)	1.3 (0.2)	1.6 (0.2)
	Other	4.0 (0.9)	5.2 (1.0)	4.6 (1.1)	4.5 (0.8)	10.5 (1.5)	11.2 (1.7)
Total		454.3 (100)	517.7 (100)	436.5 (100)	537.8 (100)	698.2 (100)	668.8 (100)

<Source: FAO, GEMS FOOD 2007>

In Korea, daily food intake per person per day was found to be 1,438g as of 2012. By gender, male and female intakes were found to be 1,630g and 1,243g respectively, indicating that male food intake is larger than female. As for intake by food group, male intake was also larger than female. However, female intake of potatoes and starches, fruits and seaweeds was larger than male. Male intake of beverages and alcoholic beverages is 315.9g, which is 1.9 times larger than female. As for meats, male intake is 1.7 times larger than female.

<Table 2_8. Food Intake per Person per Day by Korean People (Adults) >

Food	Intake (g/person/day)
Cereals	299.1
Potatoes - Starches	31.6
Sugars	10.3
Beans	36.3
Seeds	4.5
Vegetables	283.6
Mushrooms	4.9
Fruits	172.2
Seaweeds	4.9
Beverages	133.1
Alcoholic Beverages	107.3
Seasonings	34.4
Oils (vegetable)	7.9
Other (vegetable)	2.9
Vegetable Food Total	1,132.9
Meats	113.8
Eggs	25.8
Fish and Shellfish	48.7
Fats	116.5
Dairy Products (animal)	0.2
Other (animal)	0.1
Animal Food Total	305.2
Total	1,438.2
Vegetable Food Intake Rate (%)	78.3
Animal Food Intake Level (%)	21.7

<Source: Korea National Health and Nutrition Examination Survey, 2012>

<Table 2_9. Daily Intake by People Aged 1 or Older by Food Group by Gender>

(Unit: g/person/day)

Classification	Male	Female	Total
Cereals	333.6	263.7	299.1
Potatoes - starches	31.6	31.7	31.6
Sugars	11.7	8.9	10.3
Beans	41.7	30.7	36.3
Seeds	5.0	4.0	4.5
Vegetables	317.2	249.8	283.6
Mushrooms	5.1	4.7	4.9
Fruits	162.4	182.1	172.2
Seaweeds	4.6	5.1	4.9
Beverages	146.5	119.0	133.1
Alcoholic beverages	169.4	45.0	107.3
Seasonings	40.1	28.5	34.4
Oils (vegetable)	9.6	6.2	7.9
Other (vegetable)	3.0	2.8	2.9
Vegetable Food Total	1,281.7	982.2	1,132.9
Meats	141.4	85.1	113.8
Eggs	29.2	22.2	25.8
Fish and shellfish	58.6	38.8	48.7
Fats	118.3	114.3	116.5
Dairy products (animal)	0.2	0.2	0.2
Other (animal)	0.2	0.1	0.1
Animal Food Total	347.9	260.8	305.2
Total	1,629.5	1,243.0	1,438.2
Vegetable Food Intake Rate (%)	78.1	78.5	78.3
Animal Food Intake Rate (%)	21.9	21.5	21.7

<Source: Korea National Health and Nutrition Examination Survey, 2012>

In addition, as for the intake of foods by age group in Korea, the percentage of vegetable food intake displays a trend of increase according to age. On the other

hand, animal food intake displays a trend of decrease as age increases. The rates of vegetable food intake in age groups of 6 - 11 and 12 - 18 are 67.4% and 71.4% respectively and the rates of animal food intake are 32.6% and 28.6% respectively.

As for cereal intake, the largest intake is 338.9g displayed by children aged between 12 and 18 and, for vegetables, the largest intake is 364.3g displayed by elders aged between 50 and 64. The largest intake of beverages, alcoholic beverages and seasonings was by those aged 19 - 29. In terms of meat intake, the largest intake is 163.6g by children between 12 and 18 and the second largest is 159.0g by those aged 19 - 29.

<Table 2_10. Daily Intake by People Aged 1 or Older by Age Group>

(Unit: g/day)

Age	1～2	3～5	6～11	12～18	19～29	30～49	50～64	65 or Older
Cereals	190	202.7	289.7	338.9	306.0	305.6	304.7	294.7
Potato and starches	19.1	22.8	26.4	33.1	28.0	33.3	38.6	30.3
Sugars	5.1	8.8	10.2	14.6	12.8	10.3	8.4	6.1
Beans	33.8	24.3	21.3	28.7	42.3	38.4	39.9	38.0
Seeds	1.4	2.1	2.5	3.1	5.4	4.7	6.3	3.9
Vegetables	51.1	90.4	154.4	210.1	262.8	340.9	364.3	298.7
Mushrooms	1.9	2.8	3.5	4.8	78.1	5.5	3.7	2.9
Fruits	145.3	170.5	161.8	161.5	126.9	189.2	215.2	145.7
Seaweeds	2.3	3.2	3.7	4.5	3.4	6.3	5.3	4.1
Beverages	18.5	34.9	82.5	175.3	226.1	151.3	80.9	31.1
Alcoholic beverages	0.0	0.1	0.3	2.7	149.6	158.5	143.1	50.9
Seasonings	6.0	12.4	20.7	37.4	39.8	40.7	34.1	24.3
Oils (vegetable)	2.2	3.7	6.2	8.8	10.14	9.3	6.7	4.2
Other (vegetable)	0.8	1.4	6.9	2.6	2.41	2.6	3.4	2.2
Vegetable Food Total	442.4	580.3	790.2	1,026.0	1,222.3	1,296.5	1,254.6	937.1
Meats	27.1	50.4	96.6	163.6	159.0	124.7	80.1	47.8
Eggs	25.5	23.8	26.3	32.6	30.8	28.5	19.0	9.7
Fish and shellfish	14.4	19.7	29.9	35.1	45.8	64.5	54.6	35.1
Fats	285.3	255.3	234.6	179.4	126.7	81.1	65.1	48.6
Dairy products (animal)	0.1	0.2	0.2	0.4	0.4	0.1	0.1	0.0
Other (animal)	0.0	0.0	0.1	0.1	0.0	0.3	0.0	0.1
Animal Food Total	352.3	349.4	387.6	411.3	362.8	299.3	218.9	141.3
Total	794.7	929.7	1,177.8	1,437.3	1,585.1	1,595.9	1,473.5	1,078.4
Vegetable Food Intake Rate (%)	57.4	63.4	67.4	71.4	77.0	81.1	85.2	87.6
Animal Food Intake Rate (%)	42.6	36.6	32.6	28.6	23.0	18.9	14.8	12.4

<Source: Korea National Health and Nutrition Examination Survey, 2012>

As the intake of foods that are consumed frequently or in large quantities, the most frequently consumed food in Korea is white rice with daily average intake of 169.8g. It is followed by milk (75.3g) and Kimchi and napa cabbage Kimchi (60.7g).

The rankings of frequently consumed foods are relatively similar regardless of year. However, fruits produce different results by time of survey as the mainly consumed fruits vary by season.

For men, the amounts of beer and Soju intake are large, and thus are ranked in the 4th and the 5th positions respectively. For women, beer is ranked the 6th and Soju is not within the top 30. It is found that women consume fruits of various types in larger quantities than men. As for infants aged less than 1, the amount of food intake by Korean people has not been investigated. According to national health and nutrition examination survey in 2005, foods frequently consumed by infants aged between 1 and 2 are milk (182.1g), white rice (86.9g), soybean milk (56.8g), yoghurt (27.3g) and egg (17.8g). As such, livestock products are ranked at higher positions.

<Table 2_11. Foods Consumed Frequently and in Large Quantities by Korean People by Gender>

(Unit: g/day)

Rank	Male		Female		Total	
	Food	Intake g(%)	Food	Intake g(%)	Food	Intake g(%)
1	White rice	197.3 (11.9)	White rice	142.2 (11.3)	White rice	169.8 (11.6)
2	Milk	77.6 (4.7)	Milk	73.0 (5.8)	Milk	75.3 (5.2)
3	Kimchi, napa cabbage Kimchi	77.4 (4.7)	Kimchi, napa cabbage Kimchi	44.1 (3.5)	Kimchi, napa cabbage Kimchi	60.7 (4.2)
4	Beer	75.4 (4.5)	Mandarin	30.8 (2.5)	Beer	51.2 (3.5)
5	Soju	65.5 (4.0)	Apple	27.6 (2.2)	Pork	39.8 (2.7)
6	Pork	52.9 (3.2)	Beer	26.9 (2.1)	Soju	36.8 (2.5)
7	Onion	32.7 (2.0)	Pork	26.8 (2.1)	Mandarin	29.7 (2.0)
8	Makgeolli	31.6 (1.9)	Tomato	22.8 (1.8)	Onion	27.3 (1.9)
9	Cola	31.5 (1.9)	Onion	21.8 (1.7)	Beef, beef feet, beef bone broth	26.2 (1.8)
10	Beef, beef feet, beef bone broth	31.1 (1.9)	Green tea	21.5 (1.7)	Egg	25.2 (1.7)
11	Chicken	30.2 (1.8)	Egg	21.4 (1.7)	Cola	24.7 (1.7)
12	Egg	29.1 (1.8)	Beef, beef feet, beef bone broth	21.2 (1.7)	Apple	24.6 (1.7)
13	Mandarin	28.6 (1.7)	Persimmon	20.8 (1.7)	Chicken	24.5 (1.7)
14	Chili	28.4 (1.7)	Chili	20.6 (1.6)	Chili	24.5 (1.7)
15	Beef	27.2 (1.6)	Chicken	18.8 (1.5)	Tomato	21.8 (1.5)
16	Watermelon	22.0 (1.3)	Cola	17.8 (1.4)	Beef	21.4 (1.5)
17	Apple	21.7 (1.3)	Potato	17.5 (1.4)	Potato	19.3 (1.3)
18	Potato	21.1 (1.3)	Bread	17.2 (1.4)	Watermelon	19.1 (1.3)
19	Tofu	20.9 (1.3)	Cucumber	16.6 (1.3)	Makgeolli	18.9 (1.3)
20	Tomato	20.9 (1.3)	Watermelon	16.2 (1.3)	Tofu	18.5 (1.3)
21	Bread	19.3 (1.2)	Tofu	16.1 (1.3)	Bread	18.2 (1.3)
22	Ramen	18.9 (1.1)	Rice cake	15.7 (1.3)	Green tea	17.2 (1.2)
23	Cucumber	15.4 (0.9)	Beef	15.6 (1.2)	Cucumber	16.0 (1.1)
24	Fruit beverages	15.0 (0.9)	Grape	15.5 (1.2)	Persimmon	15.7 (1.1)
25	Spring onion	14.2 (0.9)	Sea mustard	14.9 (1.2)	Grape	14.5 (1.0)
26	Soybean milk	14.1 (0.9)	Fruit beverages	12.6 (1.0)	Ramen	13.9 (1.0)
27	Sparkling lemonade	13.9 (0.8)	Pear	12.5 (1.0)	Fruit beverages	13.8 (1.0)
28	Grape	13.6 (0.8)	Sweet potato	12.1 (1.0)	Rice cake	12.5 (0.9)
29	Green tea	12.9 (0.8)	Yoghurt	12.0 (1.0)	Sea mustard	12.0 (0.8)
30	Noodles	12.2 0.7)	Noodles	11.2 (0.9)	Soybean milk	11.8 (0.8)

<Source: Korea National Health and Nutrition Examination Survey, 2012>

To establish various exposure scenarios and conduct exposure assessment on especially sensitive groups, it is necessary to identify intake per person per day by age group. In particular, for livestock products, intake by infants, toddlers, children and juveniles is large. Therefore, it is important to subdivide the items for assessment.

<Table 2_12. Daily Food Intake per Person by Infants, Toddlers, Children and Juveniles >

Classification		Age	Livestock Products	Average Intake (g)	95th Percentile Intake (g)
Children	Infants and Toddlers	0-6	Beef (Korean)	2.79	18.68
			Beef (imported)	8.14	43.95
			Beef entrails	3.75	5.07
			Beef feet broth	6.99	0.00
			Pork	8.75	48.79
			Pork belly	1.50	0.00
			Processed pork (ham)	2.92	13.40
			Processed pork (bacon)	0.33	0.00
			Processed pork (canned ham)	0.46	0.00
			Chicken	5.52	45.58
			Egg	23.96	83.46
			Quail egg	0.86	0.00
			Infant formula	10.01	90.00
			Milk	135.93	425.00
			Processed milk	8.91	0.00
			Iced milk	1.40	0.00
			Ice cream	5.08	0.00
			Baby food	0.45	0.00
			Cheese	1.82	18.00
			Total	229.57	791.93
	Children	7-12	Beef (Korean)	3.73	20.11
			Beef (imported)	14.65	66.38
			Beef entrails	5.94	16.30
			Beef feet broth	8.75	0.00
			Pork	23.00	128.33
			Pork belly	12.73	74.52
			Pork entrails	0.31	0.00
			Processed pork (ham)	4.24	29.86
			Processed pork (bacon)	0.56	0.00
			Processed pork (canned ham)	2.03	0.00
			Sausage	3.04	5.70
			Chicken	12.10	72.92
			Dried chicken	4.10	0.00

			Duck	1.46	0.00
			Egg	28.03	117.44
			Quail egg	0.69	0.00
			Milk	90.31	425.00
			Low fat milk	3.30	0.00
			Processed milk	8.51	0.00
			Iced milk	1.52	0.00
			Ice cream	8.73	66.75
			Cheese	1.52	6.43
			Butter	0.23	0.89
			Total	206.41	927.84
	Juveniles	13-19	Beef (Korean)	2.64	14.16
			Beef (imported)	13.85	72.85
			Beef entrails	4.12	0.00
			Beef feet broth	5.15	0.00
			Pork	37.82	192.77
			Pork belly	15.28	95.25
			Pork entrails	0.69	0.00
			Processed pork (ham)	3.80	24.73
			Processed pork (bacon)	1.19	0.00
			Processed pork (canned ham)	1.93	0.00
			Sausage	2.43	0.00
			Chicken	17.69	113.18
			Duck	3.52	0.00
			Egg	30.08	121.94
			Quail egg	1.38	0.00
			Milk	97.28	424.00
			Milk with high calcium content	2.78	0.00
			Processed milk	10.75	0.00
			Iced milk	2.50	0.00
			Ice cream	5.64	56.40
			Cheese	1.87	6.17
			Butter	0.21	0.71
			Total	235.08	1046.94

<Source: Study on Food Intake by Infants, Toddlers, Children and Juveniles (2008), Korea Health Industry Development Institute>

<Table 2_13. Daily Maximum Intake of Infant Formula by Infants and Toddlers>

Months	Average Weight (kg)	Max. Intake (g/day)
3	5.5	129
6	7	150

<Source: Xu-Dong Jia *et al.* 2009. Assessment on dietary melamine exposure from tainted infant formula. *Biomed Environ Sci. Apr;22(2):110~113*>

❹Calculating Lifetime Average Daily Dose (LADD)

Lifetime average daily dose through food intake is calculated by considering the intake of foods that are residual in or have contaminated target substance, concentration of target substance in foods, weight and exposure period.

If data on exposure period of the target substance are not available, basic exposure periods of 70 years for carcinogens and 30 years for non-carcinogens are applied.

2-4. Risk Characterization

This is a process to decide the degree of risk on human health caused by current exposure level based on the results of hazard identification, hazard characterization and exposure assessment and thus to propose allowable amount of exposure to human body, appropriate safety management criteria or safety management goals for agricultural and animal-originated foods. Level of risk is evaluated on the basis of margin of exposure (MOE), margin of safety (MOS) and risk factors.

1) MOE Assessment

MOE is a newly introduced concept for risk assessment. Through comparison with NOAEL and EDI, the results of MOE assessment are used as a basis in deciding whether or not the dose of target substance is in a level of risk.

2) MOS Assessment

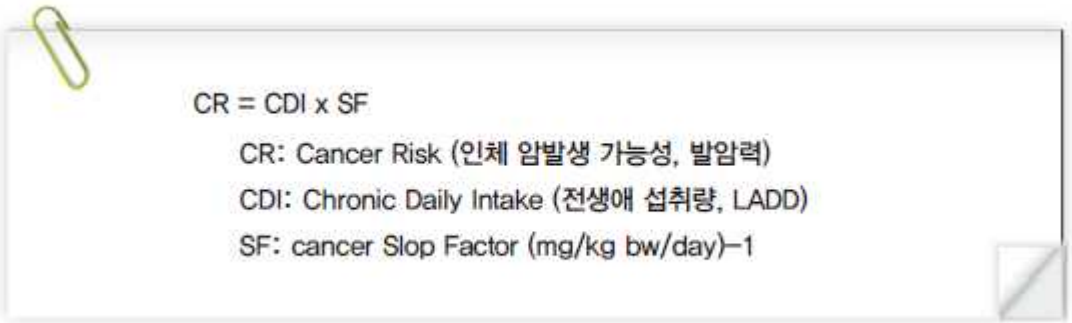
MOS is used as a ground for deciding whether or not the amount of exposure to a

target substance is in the level of risk through comparison between HBGL, such as ADI, TDI or ARfD, and EDI.

3) Cancer Risk (CR) Assessment

Cancer risk (CR) assessment is an assessment and management technique mainly used in environmental toxicological fields. CR is defined as a possibility of cancer occurrence according to individual persons' exposure to carcinogens throughout the life cycle. Risk of cancer occurrence can be decided with information about exposure to substances and carcinogenicity of the substances. Therefore, it is calculated through multiplication with specific cancer slope factor (SF) of the exposure pathway. In case of exposure to a number of carcinogens concurrently, CR of an individual is estimated in the method of calculating individual CR of each chemical and adding up the calculated values.

❶ CR Formula



❷ Assessment of Safety Management Options Using CR

In general, a value between 10 - 4 and 10 - 7 (Default: 10-6) is considered appropriate and reasonable for human health protection. If carcinogenic risk estimated considering unknown exposure is below 10-6, it can be assessed as a reasonably safe level for national health protection.

❸ Classification of Substances Carcinogenic to Human

International Agency for Research on Cancer (IARC) and EPA of the U.S. suggest criteria for determining carcinogenity of chemicals as of the following.

<Table 2_14. Classification of Chemicals according to Carcinogenicity to Human by IARC>

Category	Criteria
Group 1	The agent is carcinogenic to humans
Group 2A	The agent is probably carcinogenic to humans
Group 2B	The agent is possibly carcinogenic to humans
Group 3	The agent is not classifiable as to its carcinogenicity to humans
Group 4	The agent is probably not carcinogenic to humans

<Table 2_15. Classification of Chemicals according to Carcinogenicity to Human by EPA of the U.S.>

Category	Criteria
A	Human carcinogen (sufficient evidence of carcinogenicity in human)
B1	Probable human carcinogen (limited evidence of carcinogenicity in human)
B2	Probable human carcinogen (sufficient evidence of carcinogenicity in animal with inadequate or lack of evidence)
C	Possible human carcinogen (limited evidence of carcinogenicity in animal with inadequate or lack of evidence)
D	Not classifiable as to human carcinogenicity (inadequate or no evidence)
E	Evidence of noncarcinogenicity for human (no evidence of carcinogenicity in adequate studies)

4) Setting Maximum Residue Limit (MRL)

After setting theological maximum daily intake (TMDI) or estimated daily intake (EDI) using ADI and intake data, MRL for edible parts is set based on the results of tests on metabolism, excretion and persistence of the substance. The principles of MRL setting are as follows.

▪ In case TMDI or EDI is the same as or smaller than ADI (TMDI/EDI ≤ ADI), set the amount of residue in edible part suggested in the result of test on

persistence as MRL.

- If TMDI or EDI is larger than ADI (TMDI/EDI > ADI), this means that intake exceeds ADI. Therefore, set an appropriate MRL or postpone the permit of use by rechecking suitable metabolism, excretion and persistence test methods.

5) Recommendation of Management Options Other than MRL and Reviewing Information Limit

Risk management options are recommended based on the results of risk assessment. An example is the recommendation of safety management criteria (for allowable amounts of residue and additives) for chemical hazards in foods. In addition, permit/ prohibition of use, evaluation and proposal of alternative substances and evaluation and recommendation of reduction plans are included.

A recommendation on solutions based on analysis of the degree of information limit is also made. This is to analyze problems associated with current risk assessment information, recommend plans for securing risk assessment data in the future and propose additionally required areas of study.

3. Risk Assessment for Pesticides in Agricultural and Animal-originated Foods

3-1. Definition of Pesticide

Pesticide refers germicide, insecticide, herbicide and other chemicals prescribed by the Decree of the Ministry of Agriculture, Food and Rural Affairs that are used in prevention and extermination of germs, insects, mites, nematoda, virus, weeds and other plants and animals listed in the Decree of the Ministry of Agriculture, Food and Rural Affairs that harm all crops including shrubbery and agricultural and forest products and also drugs used to increase or suppress physiological functions of crops (Article 2, Agrochemicals Control Act).

Pesticides are used for the purpose of increasing convenience of farming, reducing farming expenses, increasing agricultural production and improving storage quality of agricultural products. However, as all chemicals are, pesticides have toxicity and exposure to them at a level higher than the prescribed can lead to toxical potency. From this standpoint, risk of pesticide means the possibility for toxical potency to be expressed at a specific level of exposure or higher and risk assessment for pesticides refers to a series of operations to digitize the degree of risk associated with pesticides, and thus to define and control characteristics of the hazard.

In the recent times, it is recommended for risk assessment to be conducted in relation to specific groups that are at a higher risk level, such as infants, pregnant women or farmers who can access pesticides easily. In addition, studies are being conducted on assessment methods to consider not only foods, but also other exposure pathways including the environment.

Of risk assessments listed in the figure below, this manual focuses on risk assessment for consumers that are exposed to hazards through food intake. Exposure to pesticides causes such toxical potencies as teratogenecity, neurotoxicity and carcinogenicity in lab animals. Toxical potencies, as such, vary according to chemical characteristics of and degree of exposure to pesticides. To prevent risk to human health and environment, each country is managing the use of pesticides through pesticide registration and permit system and handling food safety issues that can be caused by residual pesticides in foods by setting and testing MRL in foods.

3-2. Overview of Pesticide Risk Assessment

Risk assessment for pesticides is carried out through hazard identification, toxicological assessment to set reference toxicity value, exposure assessment and risk characterization. Finally, a scientific base for risk management, such as MRL setting, is provided. Hazard identification is an operation to collect and select characteristics, toxicity, exposure and dynamics data of the target substance for assessment.

The purpose of toxicological assessment in hazard characterization is to measure toxic action of pesticides on human health and the degree of toxic action. This process is based on data from animal test. For this, animal test must be conducted in various concentrations including those higher than a level allowed for human exposure.

Exposure assessment on pesticides is to estimate and evaluate the pathway of human exposure to pesticides and amount of the exposure. For ordinary people, exposure to pesticides is carried out mainly through foods and drinking water. However, people are also exposed to pesticides through skin or respiration.

At home, workers or farmers using pesticides can become exposed to pesticides unintentionally while handling pesticides. In risk assessment for residual pesticides in foods, the amount of human exposure through foods is evaluated. Therefore, selection of food intake and residual amount in food is very important. Degree of exposure varies according to type of use, chemical spraying cost, method of use, recovery and pesticide degradability and degree of transfer in environment.

Risk characterization is a process to estimate the possibility for toxic action of pesticides to be expressed in human body based on data obtained from toxicity and exposure assessments. Although toxicity and exposure data are evaluated separately, they are compositely assessed in the final stage, and thus are used in defining the degree of risk.

For risk assessment, ADI or ARfD setting through toxicity assessment and investigation on the total amount of pesticide intake through foods, such as for TMDI or EDI through exposure assessment, are necessary. Risk assessment for pesticides spread through foods (animal products) is largely divided into risk assessments for long-term hazard and for acute hazard.

Risk assessment for pesticides in agricultural and animal-originated foods is risk assessment targeting people who consume the foods. It must be carried out separately in terms of short-term hazard and long-term hazard according to characteristics of residual toxicity in pesticides.

For pesticides that last for a short period of time, ARfD is calculated using the previously described method and then international estimated short-term intake (IESTI) is evaluated. For pesticides that last for a long period of time, risk assessment for risk management options, such as carcinogenicity or non-carcinogenicity test as well as TTC, ALARA, MOS, MOE and MRL setting, is conducted as in the case of risk assessment for veterinary drugs.

1) Risk Assessment of Long-term Hazard

❶ Hazard Identification

Hazard identification for pesticides is a process to collect data on physical and chemical characteristics, such as molecular weight, melting point, boiling point, solubility, reactivity, specific gravity, density and vapor pressure, data relating to source of generation and exposure pathway, data on the amounts of production and use, data on absorption, metabolism, distribution and excretion, data on ecotoxicity and toxicity information, data on residues in crops (GAP data used) and dynamics survey data for NOAEL setting.

The table below lists assessment items for pesticide registration used by Rural Development Administration of the Ministry of Agriculture, Food and Rural Affairs.

<Table 3_1 Toxicity Test for Hazard Identification, Rural Development Administration>

Physical and Chemical Characteristics (5 items)	Persistence (2 items)	Toxicity in Human Body (18 items)	Environmental Toxicity (8 items)	Chemical Effect, Damage from Pesticide
Physical and chemical features Physical and chemical analysis report Manufacturing prescription Change on standing report Analysis report	Residue in crops Residue in soil	Acute toxicity (oral, dermal and inhalation toxicity) Irritability (skin and eye) Skin sensitization toxicity Acute delayed neurotoxicity Subacute toxicity (oral, dermal and inhalation toxicity) Chronic toxicity Carcinogenicity Reproductive toxicity Teratogenicity Genotoxicity In vivo metabolism Functional effects in human body	Acute toxicity of freshwater fish Acute water flea swimming inhibition Acute bird toxicity Acute growth inhibition Acute toxicity of earthworm Acute toxicity of honey bee Concentrated toxicity in fish Silkworm, natural enemy * Toxicity Test on Fish: Carp (international standard) used, additional tests using minnow and loach	3 or more (6 for herbicide)

❷ Hazard Characterization

Toxicity of pesticides is verified by analyzing correlation between does and response, which is the relationship between administration dose and toxic action, on the basis of the broad principle that 'all chemicals can become toxic according to their doses.'

Most toxicological effects are expressed when the dose becomes larger than a specific level. This dose is called threshold dose. Threshold dose is located in between NOAEL at which side effects do not occur in toxicity test and LOAEL at which side effects start to be expressed. Impact of pesticides on humans can be estimated by assessing how rats, mice, rabbits and dogs react to pesticides of various concentrations.

In addition, bio-mechanism of the target, such as physiological and toxicological

aspects of pesticide absorption, distribution, metabolism and excretion, must be assessed.

Based on NOAEL obtained from the most sensitive lab animals and appropriate toxicity test using data for toxicity assessment, uncertainty factor (UF) is applied considering characteristics of toxicological action, reversibility of response and differences between species and between individuals.

Then, NOAEL is divided with UF to find ADI in human. If toxicity data are incomplete, it is advisable to apply BMD in setting BMDL.

In general, UH of 100 is used based on the difference between species as 10 and the difference between individuals as 10. A value between 2 and 10 is additionally applied when NOAEL or toxicity data are considered incomplete or considering vulnerable targets, such as infants, toddlers and children. Metabolism test can be conducted using human tissue cells.

In addition, it is very important to use previously presented data or results of clinical tests on volunteers according to conditions. Lastly, results of dynamics study are the most useful data in animal - human extrapolation result prediction. Although these data can be used to obtain such information as human exposure - response prediction and impact of exposure on specific occupational groups, it is difficult to secure accurate and necessary data.

❸ Exposure Assessment

People are mostly exposed to pesticides through the intake of residual pesticides in foods. Dietary exposure assessment model for pesticides is decided according to a method to use a single exposure estimate or a method using statistical concept. However, it is fundamentally decided based on the amount of pesticides remaining in foods how much of the foods is taken.

In other words, dietary exposure assessment for pesticides is a process to estimate the total amount of pesticide intake through foods. For this, the following formula is used.

ⓐ Exposure Assessment Factor for Pesticides in Foods

This is often used to calculate tolerance and anticipated residue of pesticides in foods.

- Tolerance

Pesticide intake through foods can be obtained by investigating the actual amount of contamination by food to which pesticide is used according to directions. Maximum residue level (MRL) refers to the legally allowed maximum level of pesticide or its metabolites to remain in foods.

MRL in agricultural products is designated as the highest measurement taken from field trial on target pesticides of various regions with maximum application amount, application count and yield during the minimum period associated with the pesticides.

In agricultural and animal-originated foods, MRL is often decided by conducting residue test on livestock after supplying feeds to which pesticide was applied according to directions. If the pesticides remain in feeds, MRL is to be set for meat, milk and eggs produced from the livestock.

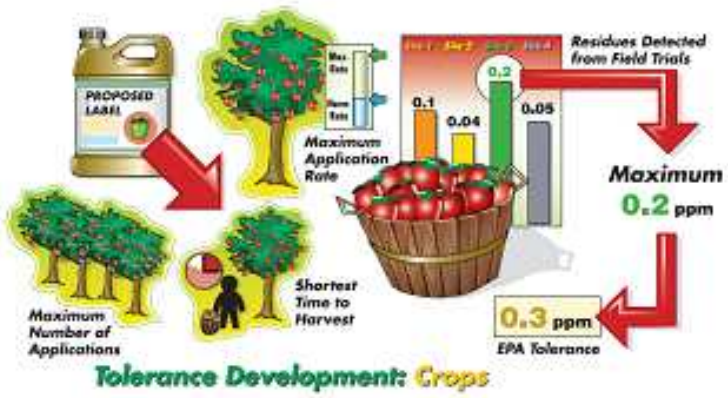
To set MRL, feeds containing pesticides in various concentrations are supplied to target animals for 28 days, residue test is conducted to investigate the amounts of remaining pesticides in edible parts of meat, milk and eggs from the target animals and the highest value found from the test is designated as MRL. However, in reality, contamination investigation results are not available in many cases.

In this case, MRL set on the basis of toxicity test results, residue test results and daily intake by food submitted at the time of the respective pesticide permit and authorization is used to estimate the amount of remaining pesticides in foods.

However, amount of pesticide residue in food is sometimes found to be lower than MRL when the pesticide is used according to directions. Therefore, the amount of total pesticide intake through foods, which is found by applying MRL, is calculated to be larger than actual exposure amount.

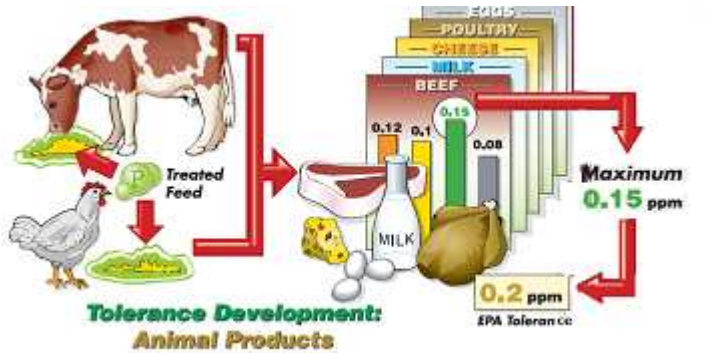
* The following is an example to set MRL for apples as shown in the figure. In

various regions (site 1- 4), the target pesticide was applied in the maximum amount and count within the suggested directions and residue test was conducted. Assuming that the residues of 0.1, 0.04, 0.2 and 0.05ppm were obtained the MRL becomes 0.2ppm.



<Fig. 3_1 Setting Pesticide Tolerance in Crops>

* As for animal-originated foods, feeds containing the target pesticide are supplied to target animals for 28 days and MRL is designated by conducting residue test on meat, milk and eggs from the animals. As in the figure below, if residues were found to be 0.12, 0.1, 0.15 and 0.08ppm in beef as in the figure below, 0.15ppm is the highest value. According to the principle of rounding, 0.2ppm is designated as MRL.



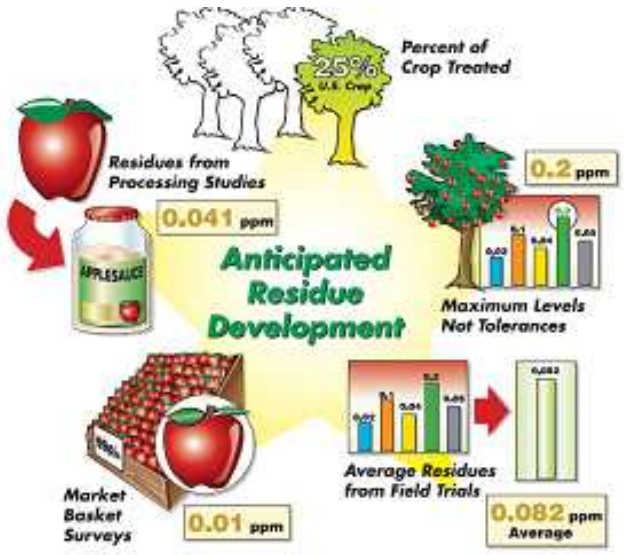
<Fig. 3_4 Setting Pesticide Tolerance in Animal Products>

● Anticipated Residue

MRL is set strictly in preparation for the worst case scenario. Therefore, in some

cases, a more realistic residue report is required. Pesticide may not have been applied according to the maximum amount and count designated, livestock products may not have been harvested at the legally allowed period following the use of pesticide and the amount of pesticide residue may have decreased over time or as a result of storage, processing, washing and cooking of the products. Supervised trials median residue level (STMR) is a residue prediction indicator that is frequently used in calculating the amount of pesticides in foods.

* For example, STMR of a pesticide is set for apples. As in the figure, if field trial produced results between 0.01 and 0.2ppm, MRL is 0.2ppm. However, STMR is 0.082ppm, the median of the value.



<Fig. 3_2 Setting Anticipated Residue>

● Food Intake

The most commonly used food intake indicators is daily average intake by food group. The pattern of food intake varies by country and region. Therefore, food intake pattern of the respective country must be taken into consideration.

On a global level, FAO (Food and Agriculture Organization)'s average food intakes and GEMS/ Food (Global Environmental Monitoring System/ Food Contamination Monitoring and Assessment Program, 2004) to list up food intakes surveyed by

dividing the world into five regions on the basis of FAO's data are available.

International data as such are associated limitations and uncertainty in themselves. However, to assess food intake within the country, it must be calculated through reference to daily average intake and ADI by age group listed in food balance sheet. If no applicable food items are found in the data for food intake estimation, intake of similar foods can be applied as intake of the respective food.

ⓑ Total Pesticide Intake through Agricultural and Animal-originated Foods (Dietary Exposure Assessment)

Total amount of pesticide intake through foods is calculated using two methods, which are TMDI, which uses MRL, and EDI that uses STMR. TDMI is calculated by multiplying MRL set for an agricultural and animal-originated food to maximum daily intake and adding the values together.

As for TMDI, crop treated amount is assumed as 100% and the degree of pesticide breakdown at the time of harvesting and during storage and cooking processes is not considered. In other words, as it is assumed that all foods for which pesticide residue are continuously treated, it reflects the maximum pesticide residue in food intake.

TMDI is a theoretic figure. As a more realistic dietary exposure assessment method, EDI is calculated by applying STMR.

To EDI calculation, STMR from field trial is applied for realistic exposure assessment. In addition, the percent of edible parts, which are actually taken, must be reflected. Moreover, in case of agricultural products, the percent of crop treated is separately quantified.

For example, when pesticide X is applied according to an appropriate dose and method to an agricultural product A and 25% of the tree from which A was produced is sprayed with the pesticide, the percent of crop treated is 25%, and thus CA becomes 1/4. In case of agricultural and animal-originated foods, it can be

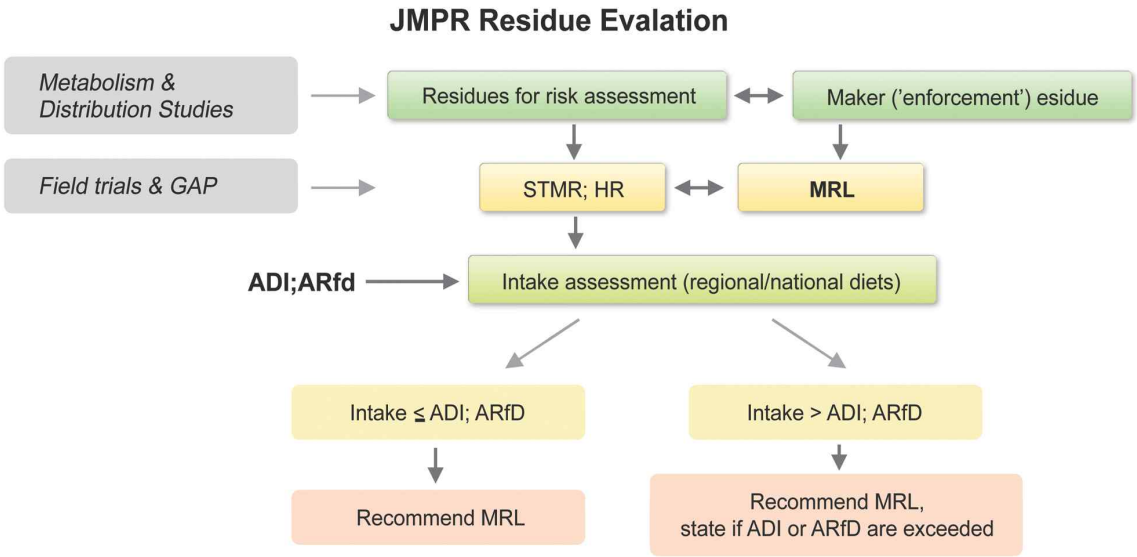
assumed that they are exposed to pesticides 100%. Therefore, CA of all agricultural and animal-originated foods is calculated as 1. The crop treated data are essential for realistic pesticide exposure assessment and must be produced through joint studies by pesticide makers, organizations to permit and authorize pesticides and risk assessment agencies.

Lastly, qualitative and quantitative changes in foods occurring during the course of processing according to physical and chemical characteristics of pesticides must also be taken into consideration.

❹ Risk Characterization

Risk characterization is a process to estimate the possibility of pesticide toxic action to be expressed in humans by examining data obtained from toxicity and exposure assessment. It is also the final stage of MRL setting. CODEX's MRL for pesticides is set in terms of extraneous MRL (EMRL) and GL (guidance level).

MRL is a standard for pesticides currently used in farming and EMRL is a standard for pesticides that are no longer used, but remain in the environment as a result of use in the past (DDT), and thus have a possibility to contaminate crops. GP is a recommendation for the degree of pesticide residue in crops when the pesticide is used according to recommended directions in case ADI is not assessed (on methyl bromide, etc.). The figure below is a schematic diagram of JMPR proposing MRL.



<Fig. 3_3 Schematic Diagram for JMPR Residue Evaluation and MRL Setting>

ⓐ Comparison of ADI and Dietary Exposure Assessment Amount (TMDI or EDI)

ADI obtained through toxicity test is compared against the assessed exposure amount.

In case exposure assessment result exceeds ADI, risk is predicted, and thus data on toxicity submitted by each country or each pesticide maker needs to be reexamined. In addition, deliberation for risk management is necessary. National theoretical maximum daily intake (NTMDI) and national estimated daily intake (NEDI) are applied for dietary risk assessment to suit the conditions of each country.

ⓑ Setting MRL

The process to set MRL for pesticide risk management must be assessed with EDI approach as in the case of veterinary drugs. If EDI is larger than ADI (EDI> ADI), metabolic and discharge test, residue test method and ADI data must be reexamined or reassessed.

If EDI is the same as or smaller than ADI (EDI ≤ ADI), MRL and withdrawal period are set. If residue data are not available, ADI is calculated considering intake of the food and, with this, provisional MRL is set.

2) Risk Assessment for Pesticides of Short-term Hazard

3)

❶ Hazard identification

In toxicity test through feed supply for 28 days or 90 days, blood toxicity, hepatotoxicity and choline esterases suppression rate caused by some pesticides are sometimes recognized as the effects triggered at the last administration rather than accumulated toxicity through long-term feed supply.

This is the case with pesticides of which absorption and discharge are fast and the speed of toxic effect recovery to normal state is fast. In case of specific pesticides with strong acute toxicity, necessity to assess safety of temporary or daily exposure has been raised. As for organophosphate or carbamate pesticides, which are highly likely to cause toxic effects in a short period of time although are low in bio-accumulation, NOAEL is calculated after one or two exposures in a short period of time (Endpoint in this case is mostly acute neurotoxicity, hematotoxicity or

toxicity inhibiting growth.).

For hazard identification or NOAEL setting for short-term hazard, data on physical and chemical characteristics, sources of generation and exposure pathways, production amount and amount of use, metabolism, toxicity, residues and dynamics study results must be collected.

❷ Hazard Characterization

Toxicity assessment of pesticides with short-term hazard is a process to obtain ARfD. ARfD is a similar concept to ADI. However, this refers to the amount of a substance at which risk to health is not detected within 24 hours from food or water intake.

In toxicity assessment, it is calculated by applying UF to NOAEL obtained through acute toxicity test. Based on NOAEL obtained from appropriate toxicity test and most sensitive lab animals using data on toxicity assessment, UF is applied considering characteristics of toxic action, reversibility of response and differences between species and between individuals. Then, NOAEL is divided with UF to calculate ARfD for humans. If toxicity data are incomplete, it is advised to apply BMD and to set BMDL.

As for UF, 100 was applied to ADI, which is obtained through long-term feed test, considering differences between species and between individuals. However, it has been pointed out that it is more appropriate to apply lower UFs to NOAEL obtained from toxicity test through single administration or administration for one day. In other words, intensity of acute toxicity is determined by determined by peak concentration (C_{max}) value of the respective substance in time - blood concentration graph and the impact of the area under the curve (AUC) is small.

In general, differences between species or individuals are considered with importance

for discharge rate or AUC. However, in case of C_{max}, the difference is small. Substances of acute toxicity are absorbed and removed quickly. Therefore, the blood concentration is restored to normal level rapidly. The toxic effect of these substances is dependent to C_{max} in blood.

Therefore, it is appropriate to apply UF smaller than 100. However, if information about factors to be considered specially and UF reduction is not available, UF of 100 is used assuming general difference of 10 between species and between individuals. JMPR sets ARfD instead of ADI and applies it to substances with strong acute toxicity and is increasing the number of applied substances gradually.

<Table 3_2 ARfD of Pesticides>

Pesticide	ARfD (ppm)	Year Established	Pesticide	ARfD (ppm)	Year Established
Acephate	0.1	2005	Lindane	0.06	2002
Adicarb	0.003	1995	Malathion	2	2003
Aminopyralid	Not necessary	2007	Mandipropamid	Not necessary	2008
Amitraz	0.01	1998	Metaflumizone	Not necessary	2009
Hydroxy-Atrazine	Not necessary	2007	Metalaxyl And Metalaxyl-M	Not necessary	2002
Atrazine	0.1	2007	Methamidophos	0.01	2002
Azinphos-Methyl	0.1	2007	Methidathion	0.01	1997
Azocyclotin	0.02	2005	Methiocarb	0.02	1998
Azoxystrobine	Not necessary	2008	Methomyl	0.02	2001
Benalaxyl	0.1	2005	Fludioxonil	Not necessary	2004
Bentazone	Not necessary	2004	Fluopicolide	0.6	2009
Bifenazate	Not necessary	2006	Fluopicolide Metabolite2,6-Dichlorobenzamide	0.6	2009
Bifenthrin	0.01	2009	Flusilazole	0.02	2007

Bitertanol	Not necessary	1998	Flutolanil	Not necessary	2002
Boscalid	Not necessary	2006	Folpet	0.2	2007
Buprofezin	0.5	2008	Glufosinate-Ammonium	Not necessary	1999
Cadusafos	0.001	2009	Glyphosate	Not necessary	2004
Captan	0.3	2007	Haloxyfop	0.08	2006
Carbaryl	0.2	2001	Hexythiazox	Not necessary	2008
Carbendazim	0.1	2005	Imazalil	0.05	2005
Carbofuran	0.001	2008	Imidacloprid	0.4	2001
Carbosulfan	0.02	2003	Indoxacarb	0.1	2005
Chlorantraniliprole	Not necessary	2008	Kresoxim-Methyl	Not necessary	1998
Chlormequat	0.05	1999	Lindane	0.06	2002
Chlorothalonil	0.6	2009	Malathion	2	2003
Chlorothalonil Metabolite Sds-3701	0.03	2009	Mandipropamid	Not necessary	2008
Chlorpropham	0.5	2005	Metaflumizone	Not necessary	2009
Chlorpyrifos	0.1	2004	Metalaxyl And Metalaxyl-M	Not necessary	2002
Chlorpyrifos-Methyl	0.1	2009	Methamidophos	0.01	2002
Clethodim	Not necessary	1999	Methidathion	0.01	1997
Clofentezine	Not necessary	2005	Methiocarb	0.02	1998
Cycloxydim	2	2009	Methomyl	0.02	2001
Cyfluthrin	0.04	2006	Methoprene And S-Methoprene	Not necessary	2001
Beta-Cyfluthrin	0.04	2006	Methoxyfenozide	0.9	2003
Cyhalothrin	0.02	2007	Monocrotophos	0.002	1995
Lambda-Cyhalothrin	0.02	2007	Novaluron	Not necessary	2005
Cypermethrin	0.04	2006	Oxamyl	0.009	2002
Alpha-Cypermethrin	0.04	2006	Oxydemeton-Methyl/Demeton-S-Methyl Sulfoxide	0.002	2002

Zeta-Cypermethrin	0.04	2006	Paraquat	0.006	2003
Cyprodinil	Not necessary	2003	Parathion	0.01	1995
Cyromazin	0.1	2006	Parathion-Methyl	0.03	1995
2,4-D	Not necessary	2001	Permethrin	1.5	2002
Ddt	Not necessary	2000	2-Phenylphenol &Its Sodium Salt	Not necessary	1999
Deltamethrin	0.05	2000	Phorate	0.003	2004
Diazinon	0.03	2006	Phosalone	0.3	2001
Dicloran	Not necessary	1998	Phosmet	0.2	2003
Difenoconazole	0.3	2007	Piperonyl Butoxide	Not necessary	2001
Diflubenzuron	Not necessary	2001	Pirimicarb	0.1	2004
Dimethenamid-P And Racemic Dimethenamid	0.5	2005	Pirimiphos-Methyl	0.2	2006
Dimethipin	0.2	2004	Prochloraz	0.1	2001
Dimethoate	0.02	2003	Procymidone	0.1	2007
Dimethomorph	0.6	2007	Profenofos	1	2007
Dinocap	0.03	2000	Propamocarb	2	2005
Diphenylamine/Dpa	Not necessary	1998	Propargite	Not necessary	1999
Disulfoton	0.003	1996	Propiconazole	0.3	2004
Dodine	0.2	2000	Propylenethiourea/Ptu	0.003	1999
Endosulfan	0.02	1998	Prothioconazole	0.8	2008
Esfenvalerate	0.02	2002	Prothioconazole-Desthio	0.01	2008
Ethephon	0.05	2002	Pyraclostrobin	0.05	2003
Ethoprophos	0.05	1999	Pyrethrins/Pyrethrum Extract	0.2	2003
Ethoxyquin	0.5	2005	Pyrimethanil	Not necessary	2007
Famoxadone	0.6	2003	Pyriproxyfen	Not necessary	2001
Fenamiphos	0.003	2002	Quinoxyfen	Not necessary	2006
Fenhexamid	Not necessary	2005	Spinetoram	Not necessary	2008
Fenitrothion	0.04	2007	Spinosad	Not	2001

				necessary	
Fenpropimorph	0.2	2004	Spirodiclofen	Not necessary	2009
Fenpyroximate	0.02	2007	Spirotetramat	1	2008
Fenthion	0.01	1997	Sulfuryl Fluoride	0.3	2005
Fipronil	0.003	2000	Tebufenozide	0.9	2003
Fludioxonil	Not necessary	2004	Terbufos	0.002	2003
Fluopicolide	0.6	2009	Thiabendazole	0.3	2006
Metabolite2,6-Dichloro benzamide	0.6	2009	Thiacloprid	0.03	2006
Flusilazole	0.02	2007	Thiodicarb	0.04	2000
Flutolanil	Not necessary	2002	Thiophanate-Methyl	Not necessary	2006
Folpet	0.2	2007	Tolylfluanid	0.5	2002
Glufosinate-Ammoniu m	Not necessary	1999	Triadimefon	0.08	2004
Glyphosate	Not necessary	2004	Triadimenol	0.08	2004
Haloxyfop	0.08	2006	Trifloxystrobin	Not necessary	2004
Hexythiazox	Not necessary	2008	Triazole Acetic Acid	Not necessary	2008
Imazalil	0.05	2005	Triazole Alanine	Not necessary	2008
Imidacloprid	0.4	2001	1,2,4-Triazole	0.3	2008
Indoxacarb	0.1	2005	Triazophos	0.001	2002
Kresoxim-Methyl	Not necessary	1998	Zoxamide	Not necessary	2007

<Inventory of IPCS and other WHO pesticide evaluations and summary of toxicological evaluations performed by the Joint Meeting on Pesticide Residues (JMPR) through 2009>

❸ Exposure Assesment

For foods that are not taken continuously, it is not appropriate to apply average intake of foods used in long-term dietary exposure assessment. Traditionally, ADI focuses on pesticide's accumulation effect and the amount of exposure to the

pesticide. Therefore, sufficient information is not provided about the exposure period. In 1997, JMPR discussed the methodologies for short-term dietary exposure assessment in relation to exposure assessment of chemicals and food intake.

As a result of the discussion, a statistical method different from long-term dietary exposure assessment using arithmetic average or median of food intakes was proposed. Monte Carlo analysis technique is used under an assumption that a series of normal distribution curves is formed when food intake and the amount of pesticide in the food are repetitively investigated.

Using the statistical analysis method, distributions of food intake and pesticide residue in food are combined, and thus the distribution of residual pesticide intake through food is derived. In short-term dietary risk assessment, variability factor for residue concentration test, maximum food intake, weight, treated crop and other factors are applied as determinant factors.

ⓐ Variability Factor (υ)

When investigating the amount of residual pesticide in food, the concentration of residue is generally calculated on the basis of mixed feed (5 - 10 feeds, 1 - 2kg/ mixed sample) where a number of feeds are mixed together. In this case, a feed with the highest residue concentration can have concentration higher by five to ten times than the average concentration of the mixed feed.

It may even exceed MRL. As for variability factor, it is assumed that there is always a sample with a higher residue concentration in all mixed feeds, and the number of food items required to satisfy the amount of feed necessary in analysis (1 - 2kg) is applied as variability factor. WHO has set and suggest variability factors for each food.

ⓑ Large Portion Size

Large portion size refers to the intake of food for one day during which the largest amount of food is taken by 97.5% of 100 persons.

WHO is collecting data from each country (Australia, France, Netherlands, Japan, South Africa, Thailand, U.K. and U.S.) on large portion size of overall population and of a group of children aged 6 or less. For dietary assessment, JMPR has also set large portion sizes for each food item (http://www.who.int/foodsafety/chem/acute_dat/en).

ⓒ Weight and Other Factors

Human weight is a factor that must be reflected in food consumption calculation. For this, refer to Chapter 1. As for other factors, edible part factor is applied under an assumption that inedible parts are always not taken in short-term toxicity assessment. In addition, if a food is cooked, processed or stored prior to intake, cooking, processing and storage factors must be applied.

ⓓ International Estimated Short-term Intake (IESTI)

Methods to calculate IESTI according to unit weight of items of which residue of target pesticides is suspected are as listed below.

▪ In case unit weight is less than 25g

Pesticide residue in mixed sample of each food item (raw or processed) reflected with the amount of residue for a single intake of the respective item can be assumed when unit weight of the food item is less than 25g. This can be applied to meat, liver, kidney, other edible parts and eggs.

IESTI = {LP x (HR or HR-P)} / bw

▪ In case unit weight is 25g or more

When a single unit amount is a single intake, as in the case with some fruits and vegetables, if residue in a single unit amount is larger than residues in mixed samples, this is a case where the item unit amount is 25g or more and, in this case, variability factor must be applied. If data on residues in foods are sufficiently available, variability factor 3, the default value suggested by JMPR in 2003, must be applied. IESTI is calculated separately for a case where large unit amount is larger than large portion size (①) and a case where unit amount is smaller (②) than large portion size.

① IESTI = U x (HR or HR-P) x υ+(LP-U) x (HR or HR-P) v / bw

② IESTI = (LP x (HR or HR-P) x υ) / bw

▪ In case there are a large number of food items or the foods have been processed

An example of this case is milk.

❹ Risk Characterization

Risk assessment on pesticides of short-term action is comprised of NOAEL, ARfD, IESTI and MRL setting assessment and calculation of the values. The values are set through comparison between short-term total intake of residual pesticide and ARfD. The procedures of short-term hazard assessment on pesticides are as illustrated in the schematic diagram below.

If the estimated acute exposure is smaller than ARfD, acute risk of the respective substance is acceptable and, considering IESTI and ARfD of the respective food, MRL is set and recommended. If not, however, that is, when IESTI is larger than ARfD, it is advised to examine risk management measures, such as restriction of use or withdrawal period adjustment, for the pesticides concerned.

4) Risk Assessment Using Tiers Approach

It is realistically difficult to conduct risk assessment on numerous pesticides. So, tiers approach is used. Tiers approach is where risk assessment is carried out in a number

of stages. Enabling to prevent budget waste, this approach is mainly used by pesticide assessment and management agencies.

For tier 1 assessment, maximum exposure and maximum intake are assumed in order to increase MOS as much as possible. The amount estimated under such conditions can be hundreds of times larger than the actual amount. However, if such an estimate is to be accepted, no more assessment is necessary.

In tier 2, actual exposure and intake amounts are applied as a more realistic situation is assumed. In tier 3, the last stage, residue monitoring data and actual intake are actively used to ensure more realistic dietary intake exposure assessment.

If exposure continues to be considered high in Tier 3, risk management measures concerning the use, such as prohibition of use and improvement on directions, must be taken into consideration.

Formula for application to exposure assessment by tiers approach

Tier 1 : TMDI = Σ Tolerance1 x F1

Tier 2 : NEDI = Σ STMR1 x E1 x C1 x P1 x F1

Tier 3 : Recalculate more realistic exposure (residue monitoring, market share and intake data used).

* Below is an example of tier application to pesticides A, B and C assuming that TMDI of the pesticides is 0.001, 1 and 3mg/kg/day respectively and ADI of the three pesticides is 1mg/kg/day. The TMDI of the pesticides below is the results in tier 1 assessment. As A's TMDI is lower than ADI, any further assessment is not necessary.

  However, B and C must be assessed again in the next tier. Assuming that EDI of pesticide B and pesticide C are assessed as 0.5 and 1.5mg/kg/day respectively, B's exposure is smaller than ADI, and thus any further assessment is omitted. Only C needs to be assessed in tier 3. In tier 3, more detailed risk assessment must be

carried out through collection or production of data, such as on actual residue and processing factors, of pesticide C.

Pesticide A(TMDIA: 0.001 mg/kg/day)

Pesticide B(TMDIB: 1 mg/kg/day)

Pesticide C(TMDIC: 3 mg/kg/day)

<Table 3_3 Carcinogenic Pesticides Categorized by EPA>

Pesticide Active Ingredient	EPA Cancer Classification	Source	Pesticide Active Ingredient	EPA Cancer Classification	Source
1,3-dichloropropene	B2	Ⅰ,Ⅱ,Ⅲ	methenyl	C	Ⅰ,Ⅱ,Ⅲ
acephate	C	Ⅰ,Ⅱ,Ⅲ	metiram(EBDC)	B2	Ⅰ,Ⅱ,Ⅲ
acifluorten(sodium acifuonfen)	B2	Ⅰ,Ⅱ,Ⅲ	metofachlor	C	Ⅰ,Ⅱ,Ⅲ
alachlor	B2	Ⅰ,Ⅱ,Ⅲ	norfurazon	C	Ⅰ,Ⅱ,Ⅲ
Alielte(fosetyl-al)	C	Ⅰ,Ⅱ,Ⅲ	oryzalin	C	Ⅰ,Ⅱ,Ⅲ
Arndro	C	Ⅰ,Ⅱ,Ⅲ	oxadiazon	C	Ⅰ,Ⅱ,Ⅲ
amitraz	C	Ⅰ,Ⅱ,Ⅲ	oxadixyl[c]	C	Ⅲ
Apollp(clofentezine)	C	Ⅰ,Ⅱ,Ⅲ	oxyfluorten	C	Ⅰ,Ⅱ,Ⅲ
arsenic acid(orthoarsenic acid)	A	Ⅰ,Ⅲ	o-phenylphenol	B2	Ⅰ,Ⅱ,Ⅲ
asulam	C	Ⅰ,Ⅱ,Ⅲ	PCNB(Quintozene)[d]	B2	Ⅱ,Ⅲ
atrazine	C	Ⅰ,Ⅱ,Ⅲ	para-dichlorobenzene	C	Ⅰ,Ⅱ,Ⅲ
benornyl	C	Ⅰ,Ⅱ,Ⅲ	parathion(ethyl)	C	Ⅰ,Ⅱ,Ⅲ
bifenthrin	C	Ⅰ,Ⅱ,Ⅲ	pennethrin	C	Ⅰ,Ⅱ,Ⅲ
bromoxynil	C	Ⅰ,Ⅱ,Ⅲ	phosmet(lmidan)	C	Ⅰ,Ⅱ,Ⅲ
captan	B2	Ⅰ,Ⅱ,Ⅲ	phosphamidon	C	Ⅰ,Ⅱ,Ⅲ
chlorobenzilate	B	Ⅰ	procymidone	B2	Ⅰ,Ⅱ,Ⅲ
cholorothalonil	B2	Ⅰ,Ⅱ,Ⅲ	pronamide(Kerb)	C	Ⅰ,Ⅱ,Ⅲ
cyanazine	C	Ⅲ	propiconazole(Tlt)	C	Ⅰ,Ⅱ,Ⅲ
cypernethin	C	Ⅰ,Ⅱ,Ⅲ	propoxur	B2	Ⅰ,Ⅱ,Ⅲ
dichlobenil	C	Ⅰ,Ⅱ,Ⅲ	Savey(hexythlazox)[1]	C	Ⅰ,Ⅱ,Ⅲ
dichlorvos(DDVP)	C	Ⅰ,Ⅱ,Ⅲ	simazine	C	Ⅰ,Ⅱ,Ⅲ
diclofop-methyl (Hoelon)	C	Ⅰ,Ⅱ,Ⅲ	terbutryn	C	Ⅰ,Ⅱ,Ⅲ
dicofol	C	Ⅰ,Ⅱ,Ⅲ	terrazole(stridiazole)	B2)	Ⅰ,Ⅱ,Ⅲ
dimethipin(Harvade)	C	Ⅰ,Ⅱ,Ⅲ	tetrachlorvinphos(Gardona)	C	Ⅰ,Ⅱ,Ⅲ
ethylene oxide	B1	Ⅰ,Ⅲ	thiodicarb	C	Ⅰ,Ⅱ,Ⅲ
Express(tribenuron methyl)	C	Ⅰ,Ⅱ,Ⅲ	thiophanate methy	C	Ⅰ,Ⅲ
folpet	B2	Ⅰ,Ⅱ,Ⅲ	toxaphene	B2	Ⅰ,Ⅲ
fomesafen	C	Ⅰ,Ⅱ,Ⅲ	TPTH(cripherytin	B2	Ⅰ,Ⅱ,Ⅲ

			hydroxide)		
lactofen	B2	Ⅰ,Ⅱ,Ⅲ	triadimenfon(Bayleton)	C	Ⅰ,Ⅱ,Ⅲ
lindane	B2/C	Ⅰ,Ⅱ,Ⅲ	triadimencl	C	Ⅰ,Ⅱ,Ⅲ
linuron	C	Ⅰ,Ⅱ,Ⅲ	tribufos(DEF)	C	Ⅰ,Ⅱ,Ⅲ
mancozeb(EBDC)	B2	Ⅰ,Ⅱ,Ⅲ	tridiphane	C	Ⅰ,Ⅱ,Ⅲ
maneb(EBDC)	B2	Ⅰ,Ⅱ,Ⅲ	triflurain	C	Ⅰ,Ⅱ,Ⅲ
methidathion	C	Ⅰ,Ⅱ,Ⅲ	zineb(EDBC)[n]	B2	Ⅰ,Ⅱ

<EPA, 2009>

A = Human carcinogen (sufficient svidence of cancer causality from human epidemiologic studies).

B = Probable human carcinogen (81=limited evidence from human epidemiologic studies,82=sufficient evidence of carcinogenicity from animal studies)

C = Possible human carcinogen (limited evidence of carcinogenicity in animals in the absence of human data)

Ⅰ. Discovery documents from People of the state of California v. Reily, Table 1 (revised). June 24, 1991.

Ⅱ. Engler, R.(U.S. EPA Science and Coordination Branch). 1991. Memo to U.S.EPA Health Effects

Division Branch Chidfs. May 22.

Ⅲ. Bureau of National Affairs. 1992. Environmental Protection Agency list of food use pesticides evaluated for carcinogenicity, compiled as of June, 1991, Chemical Regulation Reporter(August 28):1000.

a. Potenthaly oncogenic metabolils or contaminant.

b. All of this pesticide's uses have been cancelled. EPA intends to revoks its tolerances.

c. Oxadixyl is proposed new chemical.

d. Contains the carcinogen hexachiorobenzene as a contaminant.

e. All remaining uses voluntarily cancelled by manufachrer in 1990.

f. Temporary tolerances for this pesticide have expired.

g. All toxaphene uses were cancelled in 1982. However, an emergency exemption allows remaining stocks of the peslicide to be used on cotton, com, and small grains.

h. All uses of this pesticide were suspended in 1988 and have been proposed for cancelation, food tolerances are still in effect.

4. Risk Assessment for Veterinary Drugs in Agricultural and Animal-originated Foods

4-1. Definition of Veterinary Drugs

Veterinary drugs refers to drugs for animal use only and include drugs for beekeeping, silkworm farming, fisheries and pet animals (aquarium fish included). In Regulations on Veterinary Drug Handling (Ordinance of the Ministry of Agriculture, Food and Rural Affairs No. 332, Jan. 4, 2013), drugs for veterinary drug preparation are specified as veterinary material medicine satisfying criteria and standards acknowledged by the President of National Veterinary Research and Quarantine Service and feed additives added to feeds for prevention of diseases, supplementation of insufficiencies, improvement of feed efficiency and promotion of animal growth, such as vitamins, pro-vitamins, antibiotics, antibacterial agents, antioxidant, anti-fungal agents, enzyme preparations, pro-biotics, amino acid preparations and trace amounts of minerals.

Recently, a number of vaccine preparations and hormonal preparations are being developed for use through application of bioengineering technologies, such as genetic recombination. Veterinary drugs are divided into productivity improvement drugs, disease preventative drugs, diseases control drugs, disease treatment drugs and epidemic control drugs according to their purposes of use.

The characteristics are listed in the table below. Veterinary drugs are also divided into neurological drugs, antibiotics, synthetic antibacterial agents, growth hormonal agents, anti-coccidial drugs, anti-protozoal drugs and anthelmintic agents according to their efficacies.

<Table 4_1. Detailed Classification of Veterinary Drugs>

Large Category (7)	Small Category (38)	Drug (240)
Neurological drug	For action on central nervous system	Diazepam, Diprophyline, Naloxone, Benzetimide HCl, Methscopolamine
	Sedatives, anticonvulsants	Acepromazine, Azaperone, Belladonna, Brotizolam, Detomidine HCl

Large Category (7)	Small Category (38)	Drug (240)
	Analgesic, antifebrile and anti-inflammatory drugs	Ephedrin, Antipyrine, Dimethothyloxyquinazine, Aluminium salicylate, Acetaminophen, Acetanilide, Novalgin, Acetylsalicylic acid, Benzydamine, Sulpyrine
	Anti-histaminic agents	Cyproheptadine HCl, Dexamethazone, Betamethasone, Prednisolone
	Non-steroidal anti-inflammatory drugs (NSAID)	Dipyrone, Etodolac, Meloxicam, Phenylbutazone, Flunixin
Antibiotics	Aminoglycosides	Amikacin sulfate, Apramycin, Destomycin, Dihydrostreptomycin, Gentamycin, Hygromycin B, Kanamycin, Neomycin, Streptomycin, Spectinomycin
	Cephalosporins	Cefacetril, Cefazolin, Cefoperazone, Cefquinome, Ceftiofur, Cefuroxime, Cephalexin, Cephalonium, Cephaloridine, Cephapirin
	Marcrolides	Erythromycin, Josamycin, Kitasamycin, Oleandomycin, Roxithromycin, Sedecamycin, Spiramycin, Tilmicosin, Tylosin
	Penicillins	Amoxycillin, Ampicillin, Benzatine cloxacillin, Clavulnic acid, Cloxacillin, Dicloxacillin, Nafcillin, Penicillin, Penicillin G, Phenazone
	Lincosamides	Clindamycin, Lincomycin, Pirlimycin
	Peptides	Bacitracin, Colistin, Enramycin
	Phenicols	Chloramphenicol, Fluorofenicol, Thiamphenicol
	Tetracyclines	Chlortetracycline, Doxycycline, Oxytetracycline, Tetracycline
	Glycopeptides	Avoparcin, Vancomycin
	Other	Avilamycin, Efrotomycin, Bambermycin, Tiamulin, Griseofulvin, Novobiocin, Nystatin, Polymixin-B, Rifampicin, Virginiamycin
Synthetic antibacterial agent	Benzylperimidine	Ormethoprim, Trimethoprim
	Fluoroquinolones	Cenfloxacin, Ciprofloxacin, Danofloxacin, Enrofloxacin, Flumequin, Norfloxacin, Ofloxacin, Orbifloxacin, Pefloxacin, Sarafloxacin
	Quinolones	Nalidixic acid, Oxolinic acid
	Nitrofurans	Furaltadon, Furazolidon, Nitrofurazone, Nitrovin
	Sulfonamides	Dapsone, Diaveridine, Sulfachlorpyridazine, Sulfaclozine, Sulfadiazine, Sulfadimethoxine, Sulfadimidine, Sulfadoxine, Sulfaguanidine, Sulfamerazine, Sulfamethoxazole, Sulfamethoxypyridazine, Sulfamonomethoxine, Sulfanilamide, Sulfaphenazole, Sulfaquinoxaline, Sulfathiazole, Sulfatolamide, Sulfisomidine, Sulfisoxazole, Sulfithozole
	Quinoxalines	Carbadox, Olaquindox
Growth stimulati	Steroids	17B-estradiol, Testosterone, Progesterone, Norgestromet, Melengestrol acetate, Zeranol, DES

Large Category (7)	Small Category (38)	Drug (240)
on hormone	Beta-agonists	Trenbolone, Clenbuterol, Ractopamine
	Somatotropins	BST, PST
	Other	Thiouracil, Dinoprost, Carbetocin, Flumethazone, Gonadotrophin, Oxytocin
Anti-coccidial drugs	Polyethers	Semduramycin, Lasalocid, Maduramycin, Monensin, Narasin, Salinomycin
	Other	Amprolium, Ethopabate, Diclazuril, Clopidol, Nicarbazin, Halofuginone, Decoquinate, Robenidine, Roxarzone, Sulfanitran, Zoalene
Anti-protozoal drugs	Nitroimidazoles	Dimetridazole, Ipronidazole, Ronidazole
	Other	Isomethamidium, Diminazene, Berenil
Anthelmintics	Avermectins	Abamectin, Doramectin, Eprinomectin, Ivermectin, Moxidectin
	Benzimidazoles	Albendazole, Benomyl, Cambendazole, Carbendazime, Febentel, Fenbendazole, Flubendazole, Mebendazole, Oxfendazole, Oxibendazole, Thiabendazole, Triclabendazole
	Carbamates	Bendiocarb, Carbamate, Carbaryl, Methomyl, Propoxur
	Organochlorins	Lindane
	Organophosphates	Chlorpyrifos, Coumaphos, DDVP, Diazinon, Fenitrothion, Naled, Phosmet, Phoxim, Tetrachlorvinphos, Trichlorfon, Dichlorvos, Azamethiphos,
	Pyrethroids	Alphamethrin, Cyfluthrin, Cypermethrin, Deltamethrin, Fluvalinate, Tetramethrin
	Piperazines	Piperazine, Pyrantel
	Saliicylamides	Niclosamide, Oxyclozanide
	Other	Aluminium silicate, Cymiazole, Clorsulon, Chlorophenol, Closantel, Dichlorophene, Diethylcarbamazine, Diphenhydramine HCl, Nitroxynil, Amitraz, Methoprene, Difluron, Levamisole, Fluazuron, Imidacloprid, Oxythioquinox, Pyremethamine, Morantel, Clioquinol, Cyromazine
Total	38	240

<Source: Veterinary Drug Handbook (2001), Veterinary Drug Efficacy Classification (2004)>

4-2. Overview of Risk Assessment for Veterinary Drugs

Risk assessment is carried out to protect the health of consumers that take foods originated from livestock on which veterinary drugs have been used. In other words, this is a process to protect consumers' health by setting acceptable amount of human exposure to veterinary drug by each edible part of animal-originated foods that does

not cause any harm even when humans are exposed to it on a daily basis for the entire lifespan.

Veterinary drugs are used intentionally to treat livestock diseases or to improve livestock productivity. Therefore, in risk assessment, hazard identification and hazard characterization can be carried out based on data submitted by companies developing the drugs. In case of probiotics, antibacterial agents and antiseptic agents, risk assessment can be limited to intake through foods or, in case of exposure assessment, to livestock species for which the respective veterinary drugs are used. Therefore, the complicated process to review the sources of exposure, as in the case of contaminants, can be omitted.

Therefore, hazard characterization is carried out mostly on the basis of toxicological, pharmaceutical and bio-dynamics data about the respective veterinary drug. For veterinary drugs, not only teratogenicity, mutagenicity or carcinogenicity, but also pharmacological characteristics and the possibility of allergic reaction are taken into consideration for risk assessment. In case of antibiotics, antibacterial agents and antiseptic agents, microbiological risk for normal intestinal flora caused by intake through foods must also be considered.

Risk assessment for veterinary drugs is carried out through the process of hazard identification, hazard characterization, exposure assessment and risk characterization. As for the method of assessment, endpoints are assessed by examining the previously described animal/ human toxicity test data. It is followed by deciding NOAEL or BMDL for each drug. Then, the most appropriate NOAEL or BMDL is selected and ADI for chronic human exposure is calculated using SF and UF.

When details concerning veterinary drug absorption, distribution and discharge in edible parts are decided based on analytic and toxicological understanding, the amounts and levels of original substance or metabolite residues are set. Lastly, MRL is set and it is analytically checked that the level of veterinary drug in edible parts does not exceed ADI. However, in case of veterinary drugs that act as genotoxic substances affecting DNA and carcinogens, ADI and MRL cannot be set.

So, it is advisable to assess these drugs using MOE, which is expressed with the ratio of minimum dose at which reaction is displayed to predicted dose to which human exposure is acceptable. In addition, following risk assessment on veterinary

drugs, risk management plans including whether or not use of the drugs is allowed, precautions for use, safe withdrawal period and MRL in foods must be suggested.

4-3. Veterinary Drug Risk Assessment Stages

Veterinary drug risk assessment is conducted in stages specified in Table 4-2 below. In the stage of risk assessment preparation, related data are collected and, through information exchange, risk assessor and risk manager decide whether or not to conduct risk assessment and the status of data use.

When it is decided to carry out risk assessment, the assessment is implemented in the stages of hazard identification, hazard characterization, exposure assessment and risk characterization. When risk assessment is completed, risk communication activities are performed, such as to draw up a report for risk management options, and thus risk management is implemented. This manual describes a process when risk assessment is decided for implementation.

<Table 4_2. Veterinary Drug Risk Assessment Stages>

Assessment Stage		Description
Preparation for Risk Assessment	Collecting related data and deciding risk assessment implementation	Collect data on veterinary drug basic characteristics, pattern of use, metabolism, pharmacological properties, toxicity, sampling and analysis method, residue and excretion → Risk prediction to decide data use and risk management implementation
Risk Assessment	Hazard identification	Toxicity test, selection and assessment → Carcinogenicity and predicted risk assessment
	Hazard characterization	Apply uncertainty factory following NOAEL and BMDL setting → Calculate ADI
	Exposure assessment	Residue test on target livestock → assess human exposure considering intake of edible parts
	Risk characterization	Assessment of safe concentration by edible part specified by the Ministry of Agriculture, Food and Rural Affairs, withdrawal period, MRL by edible part and precautions for use
Risk Communication	Risk information exchange for risk management	Suggest HBGL and MRL and provide scientific advice on risk prediction and potential risk → Draw up report for risk management options and exchange information through meeting

1) Hazard Identification

This is a stage to identify hazard of residual veterinary drugs in foods. Risk prediction and assessment is carried out by reviewing data on characteristics of the target veterinary drug ((Q)SAR data), pharmacological data (absorption, distribution, metabolism, excretion, bio-accumulation and PBPK/ PBTK models), bio-dynamics data, toxicological data (animal and human test), data on human exposure, internationally recognized papers (SCI papers), study reports published by foreign regulatory organizations (WHO, IPCS, FAO, JECFA, JMPR, IOMC, IARC, OECD, EPA, FDA, NTP, ATSDR, EU Committee and Dept. of Health and Human Services in Japan), toxicity information risk profile, government reports and monographs. Therefore, human exposure dynamics study data are very important in assessment.

However, human exposure dynamics studies successfully conducted in line with the respective situations are almost not available. As a result, in most cases, animal test is carried out by GLP organizations according to OECD test guidelines or data from the animal tests conducted are used. Animal test data as such are comprised of information on toxicity of veterinary drugs, duration of toxicological action, dose dependence, reversibility or irreversibility and differences between species and between sexes. Considering species and count of animals used in the test as well as administration pathways, administration doses, administration periods, dose responses and side effects, the results can be extrapolated to humans.

Toxicity test data are largely divided into general toxicity test, special toxicity test and other toxicity test data.

As general toxicity test data, results of acute oral toxicity test and repetitive administration toxicity test are used. From acute oral toxicity test, LD50 is suggested. From repetitive administration toxicity test, toxicological endpoints and NOAEL are obtained. Special toxicity tests include teratogenicity, reproductive ability, fetal toxicity, immunogenicity, neurogenicity, mutagenicity and carcinogenicity tests. For all of these tests, NOAEL can be set per item. In particular, mutagenicity and carcinogenicity test data are necessary in assessing substances as genotoxic carcinogens. Other toxicity test data include data about microbiological toxicity of residues for normal intestinal flora and impact on humans. The data on microbiological toxicity of residues can suggest NOAEC at minimum growth

inhibition dose for normal intestinal flora through human or verified animal test models and tests using test tubes.

<Table 4_3. Types and Characteristics of Toxicity Tests on Veterinary Drugs>

Large Category	Toxicity Test Items	Characteristics
General Toxicity Test	Acute Toxicity Test	• Target drug is administered orally and non-orally once to male and female animals of two species or more. Then, the animals are observed for 1 - 2 weeks and the displayed toxicity is quantitatively and qualitatively searched. • To estimate intensity of toxicity by calculating 50% of fatal dose (LD_{50})
	Subacute Toxicity Test	• Target drug is administered daily for three weeks or longer (3 - 6 months for feed additives) orally or through clinical application pathways to male and female animals of one species (two species for feed additives). Then, the displayed toxicity is quantitatively and qualitatively searched. • To find toxic amount, min. toxic amount and NOAEL • To observe animals' general conditions, weight, feed and sample intake and amount of water intake, to conduct urine test and ophthalmologic test, to visually check organs and tissues upon completion of administration (observation), to conduct histopathological test when necessary, to administer hematological and blood biochemical examinations during autopsy, to measure specimen or metabolite residues in muscle, fat, liver and kidney
	Chronic Toxicity Test	• Target drug is administered daily for three months (two years for feed additives) orally or through clinical application pathways to male and female animals of one species (two species for feed additives). Then, the displayed toxicity is quantitatively and qualitatively searched. • To calculate the amount of drug at which toxical changes occur and NOAEL • To observed animals' general conditions, weight and feed and sample intake, to conduct urine test and ophthalmologic test, to visually check organs and tissues upon completion of administration (observation), to measure weight and administer histopathological test, to conduct hematological and blood biochemical examinations during autopsy
Special Toxicity Test	Reproductive Toxicity Test	• Test for impact on reproductive process, such as reproductive ability of lab animals and their posterity • Teratogenicity test Target drug is administered every day during organogenesis period of the fetus orally or through clinical application pathways to female animals of one each of rodent and nonrodent species. Then, death of embryo and fetus as well as weight, growth, functional development and morphological abnormalities of the surviving fetus are searched. • Reproductive toxicity test on a generation of animals or their posterity

		The target drug is administered every day orally or through clinical application pathways to male and female animals of one species or more in one or multiple generations from before breeding (for rodents, 8 weeks or longer from the 8th week) to during breeding, during pregnancy and during weaning period of the newborn. Then, impact on mating rate, conception rate, delivery date, birth rate, rate of survival on day 4 and weaning rate is searched.
	Genotoxicity Test	• This is a test to search whether or not the target drug causes genetic mutation. Genetic markers, such as changes in gene regulation, chromosomal level and DNA level, are searched. • In general, 'reversal mutation test using bacteria' with genetic mutation induction as an indicator and 'in vitro chromosomal abnormality test using mammalian cultured cells' and 'in vivo micronucleus test using rodent hemoblast' with chromosomal abnormality induction are conducted.
	Carcinogenicity Test	• To be conducted for substances of which chemical structures or pharmacological actions are similar to already known carcinogens or substances suspected of carcinogenicity, when result of short-term carcinogenicity test, such as mutagenicity test, is found to be positive, or when carcinogenicity is suspected as a result of toxicity test • Target drug is administered daily for 18 - 24 months or longer orally or through clinical application pathways to male and female animals of two species or more. Then, cancer (malignant tumor) occurrence status is quantitatively and qualitatively searched. • To observe general conditions and weight of animals, visually check organs and tissues upon test completion and conduct histopathological test to search the status of tumorous lesion occurrence • When necessary, peripheral blood is collected during autopsy. With the collected blood, red/ white cell count is measured and smear test is conducted.
Microbiological Toxicity Test	Test for impact on normal intestinal flora	• To search impact of antibiotic and antibacterial substances in foods on normal intestinal flora • MIC test using normal intestinal flora communities (at least 100 strains of 10 types) originated from human feces with suppression of intestinal mucosa defence, expression of resistant bacteria and metabolic disorder caused by anti-biotic and anti-bacterial agents in foods, test on anaerobic flow culture system for normal intestinal flora and test using mice with normal intestinal flora expression
Immunotoxicity Tests	Immunotoxicity Test	• In case abnormalities are suspected in immunological functions and immunity organs as a result of subacute or chronic toxicity test • A single gender of SFP mice or rats expected of sensitive reaction can be selected. Ten animals each in test and control groups are administered daily for 30 days or longer and the expressed toxicity is qualitatively and quantitatively observed (humoral immunity test, specific cellular immunity test and non-specific cellular immunity test included)
	Antigenicity Test	• For high-polymer protein type veterinary drugs of systemic effect and

		drugs with possibility to function as hapten despite being low polymer substances • Anaphylactic shock response test (guinea pigs) and passive anaphylaxis (Heterogenous: Mice, Homeogenous: Guinea pigs)
	Skin Sensitization Test	• For drugs that can cause abnormal immune reaction in immune system through contact with human or animal skin mucosa accidently or intentionally according to their characteristics • Skin sensitization test using guinea pigs, local lymphatic node proliferation test using mice and other skin sensitization tests included
Other Special Toxicity Tests	Other Special Toxicity Tests	• Tests necessary according to characteristics of drugs, such as usage and formulation • Other special toxicity tests include inhalation toxicity test and endocrine disruption test.

2) Hazard Characterization

Veterinary drugs can be assessed using noncarcinogenic and carcinogenic assessment techniques according to target substances in the stage of risk characterization. In case the target veterinary drug is a noncarcinogenic substance, noncarcinogenicity assessment is carried out based on appropriate data (animal toxicity test) selected in the stage of hazard identification.

The most acute toxicity markers are selected through dose - response assessment, and thus LOAEL, NOAEL and BNDL are set. As for BMDL in this case, 5% or 10% confidence interval is set according to the applied test model. When appropriate model is selected for data, calculation can be carried out conveniently using BMDS program of EPA.

This manual recommends BMD approach, which is set through statistical calibration. Lastly, to set ADI, which is HBGL, UF is applied in order to calibrate uncertainty in the course of extrapolation aimed at application of animal test results to humans. Veterinary drugs require microbiological ADI in addition to toxicological ADI.

When ADI is set based on the results of toxicity tests on lab animals or using test tubes, it is called toxicological ADI. In addition, when it is set on the basis of impact on normal intestinal flora as in the case of antibiotics and quasi-compounds, it is called microbiological ADI.

In risk assessment for veterinary drugs, microbiological ADI is used as more

important information. In general, the lower of the two ADIs is used as ADI for MRL setting.

Carcinogenicity test must be carried out after assessment to determine whether or not the target veterinary drug is a genotoxic substance causing genomic abnormality, a substance causing cellular proliferation or a 'genotoxic carcinogen.' If there are evidences that the target veterinary drug is a genotoxic carcinogen (highest importance placed on dynamics study data), it must be prohibited of use and the detection limit in analysis must be set as the lowest possible exposure.

This is ALARA (as low as reasonably achievable) assessment management technique. If a veterinary drug is not a genotoxic carcinogen, assessment can be carried out using TTC assessment, linear extrapolation assessment and BMD assessment techniques.

If the target veterinary drug is a carcinogen, but animal test data for assessment are not available, TTC of the drug can be estimated using chemical structure - carcinogenicity intensity relationship. If the structure is cyano-, diazo- and quaternary nitrogen, which are known as highly toxic carcinogens, the drug is categorized into Class III. In addition, if the structure is simple and the structure is in between the two, the drug is categorized into Class I and Class II respectively.

When class is designated, assessment and management are conducted by applying human exposure threshold at 5% response dose of NOEL response curve by class as maximum estimate for humans. This is TTC assessment technique. Assessment using BMD technique is carried out the same as assessment of noncarcinogens. After BMDL is derived, POD is set. Then, it is divided with UF to set HBGV.

3) Exposure Assessment

For exposure assessment, this manual suggests standard data on the currently applied age classification, average life expectancy, average weight and food intake of Korean people. Table 4 below shows classification of Korean people as well as their average weight and the top 95th percentile weight. Average life expectancy is set as 70 years of age.

For livestock product intake per person per an adult Korean (meat, fish and

shellfish), food balance sheet (2007) is referenced. As for food intake per person per day by age group, a table on distribution of intakes per person per day for infants, toddlers, children and juveniles is used for reference.

For human exposure to veterinary drugs through livestock products, four scenarios can be assumed. First, a scenario for exposure through all animal-originated food groups or animal-originated food items is mainly used for assessment of human exposure to chemicals contaminating animal-originated foods or detailed food items.

For this, information of adults' average weight, average age and average intake of each food item is used. Second, a scenario for exposure by specific age group is used when assessing exposure to harmful chemicals, such as melamine, by sensitive age groups, such as infants and toddlers. In this case, average weight and average intake of the specific age groups (infants and toddlers) must be applied.

Third is a scenario of exposure by people with large intake or 95th percentile intake of specific livestock products. In case of a large intake of foods, especially with high toxicity, assessment of human exposure to harmful chemicals through the foods must be carried out using the top 95th percentile intake data.

The last is an exposure scenario without any information. This is for a case in which data on food items and intake amounts are not available. In this case, human exposure assessment is conducted based on ordinary adults' average age and average weight by assuming that daily intake of ordinary adults is 3kg (1.5kg of solids and 1.5kg of liquid). After close examination of the data, one of the four scenarios above is selected. Then, daily human exposure must be calculated using the tables below.

As an example, exposure of Korean adults (D) to veterinary drug A (1mg/kg) used in pigs (100kg) is calculated below. For this, C, CRi, BW, n, AT and F are assumed as 0.001mg/g, 51.07g/day, 70kg, pork 1, and 30 years. As for ED, it is set as 60 years assuming intake for 30 years. Then, daily human exposure (D) is calculated as 0.001㎎/㎏ x 51.07g/day x 1 x 60year / 70year x 70㎏ to 0.001㎎/㎏ /day. This value is used as a human exposure assessment value in the stage of risk characterization.

Mammals		Poultry		Fish		Honeybee	
Muscle	300g	Muscle	300g	Muscle and skin	300g	Honey	20g
Fat	50g	Fat	50g				
Liver	100g	Liver	100g				
Kidney	50g	Kidney	50g				
Milk	1,500g	Milk	1,500g				

4-4. Risk Characterization

This is a process to calculate risk of hazard. After the degree of risk is identified, tolerable human exposure to hazard in agricultural and animal-originated foods and appropriate safety management criteria or safety management goals are suggested. With the values, risk management is conducted.

First, carcinogenicity of the target veterinary drug must be assessed. If the drug is a carcinogenic substance, it must be assessed separately as genotoxic carcinogen displaying carcinogenicity and genotoxicity and non-genotoxic carcinogen without genetic toxicity. Substances with high carcinogenicity and genotoxic carcinogens must be prohibited of use and managed with ALARA to set the lowest possible exposure (analysis detection limit).

On the other hand, simple carcinogens for which thresholds can be set, the substances are divided into a group of 1.8mg/person/day or higher and a group of 0.54- 1.8mg/person/day and 0.09mg/person/ day or lower based on human exposure thresholds categorized with TTC assessment technique. Then, the substances are assessed as toxic substances with low, medium and high carcinogenicity. In addition, CR must be calculated. CR is set by multiplying CDI (lifetime average intake) of the target veterinary drug with SF $(mg/kg\ bw/day)^{-1}$. As for SF, cancer slope factor for substances assessed by US EPA-IRIS can be applied.

In general, substances with CR between 10^{-4} and 10^{-7} are assessed as substances with no significant risk. MOE enables to take into consideration matters concerning risk management of the target veterinary drug as assessment is carried out by reflecting human exposure assessment as much as possible. This is a new assessment technique used in risk assessment. In fact, it is implemented compulsorily by US-EPA in risk

assessment. The formula of MOE setting is BMDL/ LADD of the target veterinary drug. When MOE is 100 or higher (MOE > 100), it is assessed as a n acknowledged safe level.

In addition, it can be used in risk assessment of veterinary drugs of which toxicological threshold cannot be set. When MOE of genotoxic carcinogen is 10,000 or higher (MOE > 10,000), it is assessed as acknowledged safe level and risk management can be conducted. As for MOS, it is set by dividing ADI that takes into consideration exposure pathways with the amount of exposure to the target veterinary drug.

As a result of MOS calculation, if HI is found to be smaller than 1 (MOS < 1), it indicates that there is a possibility of risk generation. If HI is larger than 1 (MOS > 1), there is no possibility for risk to be caused and the current exposure level is acceptable. Lastly, when the target veterinary drug is used on food animals, MRL and withdrawal period must be set.

MRL of veterinary drugs means the legally allowed maximum residue concentration (㎎/㎏ or ㎍/㎏) of substances inside or on the surface of livestock products as a result of the use of veterinary drugs on livestock.

When setting MRL, impact on public health and food processing must also be considered together with ADI. In this manual, Food Basket model recommended by WHO and EDI approach are used for MRL setting. Important factors in deciding MRL are ADI (or TDI or ARfD), weight of people taking the food, pattern of food intake, marker residue, percent of marker residue to total residue and distribution in organs.

For MRL setting, safe concentration by edible part is calculated considering daily intake by edible part of each livestock species and average adult weight. The formula given below and, as for the intake by edible part used in this calculation, CODEX' standard intake data are used.

Next, residue test must be conducted on the respective drug or the related data must be secured. Residue test data are comprised of drug test data, excretion test data and residue analysis technique. In particular, using pharmacokinetics test data, chemical characteristics of residues in the tissue of edible parts (binding or free), residue

concentration, marker residue and maximum residue level (draft) can be assessed. Using residue excretion test data, time of residue excretion from edible part and withdrawal period are assessed.

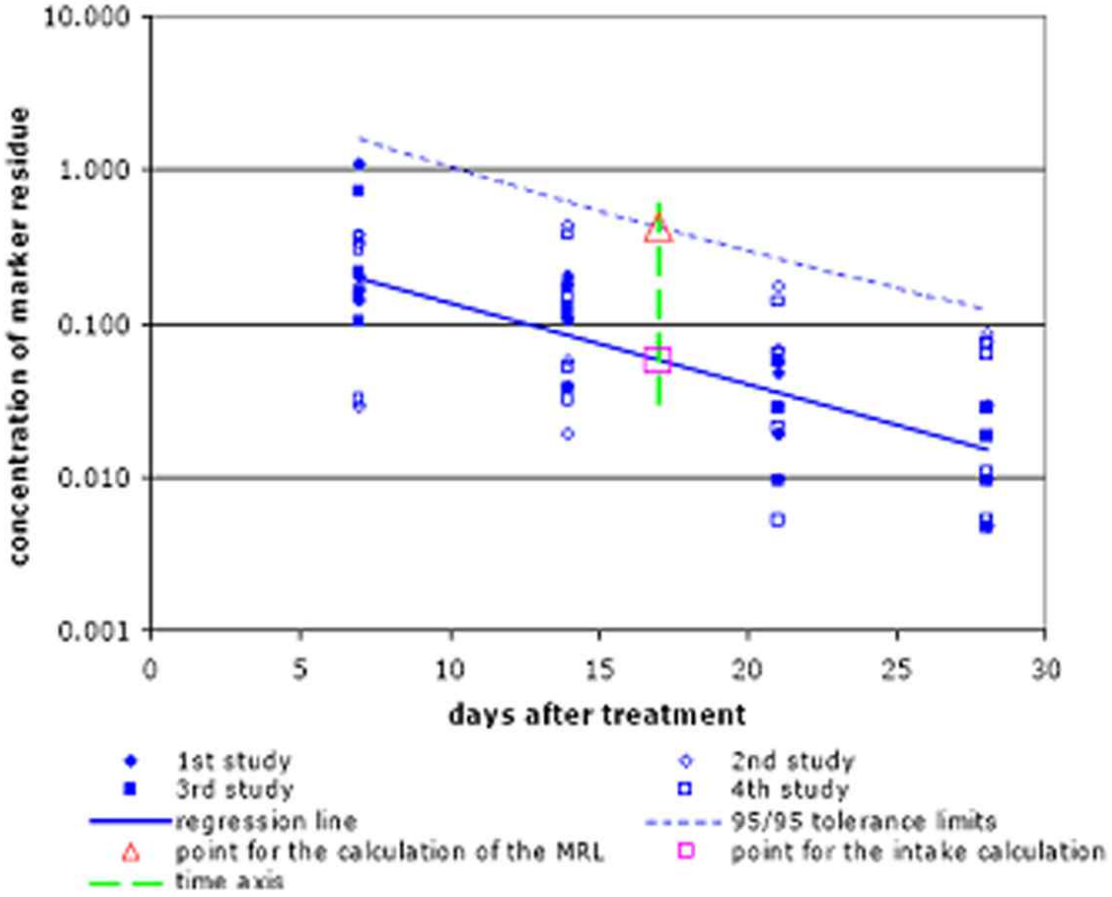
Lastly, data on residue analysis techniques must specify singularity, accuracy, precision, reproducibility and usability of analysis technique, sensitivity to as well as safety, detection level and limit of quantification of inhibitors so as to describe and certify marker residue analysis technique, and thus demonstrate that the technique is applicable.

In case total residue amount is found to be smaller than or the same as ADI and amount of residues in each edible part is found to be smaller than or the same as safe concentration set on the basis of the residue test results, maximum residue amount is set as MRL (draft) for the respective part.

Therefore, percent of marker residue to total residues, time point at which total residue intake is lower than ADI in livestock products and distribution of residues by organ are important factors determining MRL.

On the other hand, MRL for milk must not exceed ADI and also maximum concentration at which impact is not exerted on starter culture used in milk processing must not be exceeded. MRL (draft) set through this process is multiplied by intake of each edible part and again multiplied with a value calculated by dividing TR (total residue) with MR (marker residue) in each part with TR (total residue). Then, the values for each edible part are added up to find theological maximum daily intake (TMDI).

Estimated daily intake (EDI) is calculated by multiplying average residue when residue is smaller than or the same as ADI and residue in each edible part is smaller than or the same as the set safe concentration with intake of each edible part, again multiplying it with a value calculated by dividing TR with MR and then adding up the values for each part. In other words, the value above dotted line (95% tolerance limit) in the figure below is used as MRL (draft) for TMDI and the dotted line (average of measurements) is used as MRL (draft) for EDI.



<Fig. 4_1 Changes in Residue Concentration in Edible Parts over Time>

When TMDI or EDI is lower than or the same as ADI (TMDI or EDI ≤ ADI), it becomes MRL.

In general, EDI set as MRL is between 40 and 70% of ADI. In case EDI is larger than ADI (TMDI or EDI > ADI), intake exceeds ADI, and thus MRL must be decided again by conducting metabolic and excretion test, checking residue test method check and re-checking and re-assessing ADI data (Fig. 4_3). International organizations, such as JECFA, consider that EDI approach is more realistic, and thus are mainly using it in MRL setting. In this manual, EDI is also used in MRL setting.

When MRL is set, the last process is to set withdrawal period for the target

veterinary drug. Withdrawal period must be set based on ADI, safe concentration and MRL of the drug. For this, the drug is administered to target animals and the period during which the residue of drug falls below MRL by edible part is set as withdrawal period. A general practice is to set longer time than the actual period considering individual differences.

As an example, MRL of a veterinary drug A (Marker Residue: A) administered to cattle at the ADI of 10㎍/㎏ bw/day is set below. The amount of intake by a person with both weight of 60kg is 600㎍/person/day.

Accordingly, the safe concentrations suggested for each part are Muscle: 10㎍/㎏ bw x 60㎏ /day ÷ 300g/day= 2㎍/g/day (ppm), Liver: 10x60÷100=6ppm, Kidney: 10x60÷50=12ppm, Fat: 10x60÷50=12ppm and Milk: 10x60÷1500=0.4ppm. It is assumed that this drug was administered to the animal according to Good Veterinary Drug Practice (GVDP), residue test was conducted (three times) and the results in the table below were obtained.

<Table 4_4 Residue amount in edible tissues>

<n=3, Unit ppm>

Average Residue	1 hour later	1 week later	2 days later	3 days later	4 days later
Muscle	50	20	10	5	0.5
Liver	200	150	50	10	0.5
Kidney	200	150	30	5	0.5
Fat	50	5	2	1	0.1
Milk	100	10	5	0.1	0.05

When residue by part is lower than safety dose, the value is that of three days later. As for the total intake in this case, EDI is 305ppm, which is the sum of Muscle: 0.5x300=150ppm, Liver: 0.5x100=50ppm, Kidney: 0.5x50=25ppm, Fat: 0.1x50=5ppm and Milk: 0.05x1500=75ppm. This value must not exceed 600ppm, the ADI. As for EDI of veterinary drug A, 50% of ADI is considered appropriate. Finally, MRL of

veterinary drug A on cattle is 500ppb in muscle, 500ppb in liver, 500ppb in kidney, 100ppb in fat and 50ppb in milk and the withdrawal period is at least two days.

<Table 4_5 Example of Assessment on Veterinary Drug A>

Average Residue (Cattle)	Safety Dose (ppm)	MRL, Day 2 (ppm)	MT/AT	Intake (g)	EDI(ppm)
Muscle	2	0.5	1	300	305
Liver	6	0.5	1	100	
Kidney	12	0.5	1	50	
Fat	12	0.1	1	50	
Milk	0.4	0.05	1	1500	

ADI: 600 μg/person/day

EDI: 305 μg/person/day (50% of ADI)

MRL: Muscle: 500 μg/kg

Liver: 500 μg/kg

Kidney: 500 μg/kg

Fat: 100 μg/kg

Milk: 50 μg/kg

Withdrawal Period: 4 days

5. Risk Assessment for Environmental Contaminants in Agricultural and Animal-originated Foods

5-1. Overview of Risk Assessment for Environmental Contaminants

Contaminant refers to all substances unintentionally transferred to foods. It includes all substances and natural toxins (fungal toxin) existing in foods that have been originated from environment as well as the process of production (grain processing, livestock product processing and treatment drugs), manufacturing, processing, packing and transfer. Examples include melamine and heavy metals.

However, veterinary drugs or pesticides, microbial toxins (bacterial toxins) and processing supplements used in relation to food production are excluded. CODEX' contaminant and toxicity risk assessment is comprised of hazard identification to identify hazards, hazard characterization to analyze characteristics of the hazards, exposure assessment to assess human exposure to the substances and risk characterization to indicate the degree of risk and possibility for the risk to be expressed in numbers.

In other words, risk assessment on contaminants is a series of operations to decide safety factors and to compare exposures and provisional intakes in order to decide NOAEL and LOAEL and to set tolerable daily intake (TDI), tolerable weekly intake (TWI) and tolerable monthly intake (TMI).

This is also a process to develop risk management measures, such as to set MRL of contaminants in foods or to develop management guidelines for contamination sources. As such, risk assessment for environmental contaminants is similar to that for pesticides or veterinary drugs. Therefore, risk assessment on environmental contaminants conducted by CODEX is described below.

5-2. Risk Assessment of Environmental Contaminants in Agricultural and Animal-originated Foods

1) Hazard Identification

This is a process to predict and decide side effects or risks caused by environmental contaminants.

The indicators for final decision in this stage are mortality, impact on reproduction and generation, neurotoxicity and toxicity on specific organs, which are similar to those for other chemicals (veterinary drugs and pesticides). These data are obtained from clinical case report on humans, clinical trials, dynamics studies or animal test results.

The most important part of this stage is to combine a phenomenon with its cause and to verify appropriateness and intensity of the combination. Indirect test, such as the one using test tubes, can also be of significant help. For environmental contaminants, it is difficult to find test and study data unlike in the case of veterinary drugs and pesticides for which the makers provide such data. Therefore, examination of the implemented risk information or risk profile is preferentially conducted.

If risk information or risk profile is not available, domestic and international literatures or information from related organizations must be searched. In CODEX, the Codex Committee on Food Additive and Contaminants (CCFAC) draws up position paper in relation to proposals from member states or environmental contaminants of which risk has been identified.

Position paper, as such, describes not only toxicological data, but also analysis-related data, issues concerning food trade and technical and economic aspects of risk management in detail.

In addition, position paper includes MRL for the respective substances in each member state. CCFAC requests JECFA, an organization of the related experts, to conduct risk assessment in order to investigate risk to human health caused by contaminants.

2) Hazard Characterization

This process is the same as hazard characterization for risk assessment on veterinary drugs or pesticides. This is a process to quantitatively or qualitatively assess risk characteristics of the target environmental contaminant. With chemical structure and

metabolism of the contaminant in food taken into consideration, dose - response assessment is conducted in this process to quantitatively indicate biological response relationship with the amount of contaminants taken.

For the assessment, calibration factors, such as exposure intensity, age, gender, administration pathway, species and exposure pathway, are taken into consideration.

In this process, extrapolation is carried out from animals to humans and from higher dose to lower dose. Although extremely difficult, it is essential in estimating the predicted dose with which response is forecast and also the possibility of occurrence in humans as almost all data are obtained from animals. However, as the predictions are based on a limited number of animal tests, they may be inappropriate for human response to exposure.

Therefore, in this stage, a large number of assessment models and assessment methods are examined and the characterization is carried out on the basis of decisions about uncertainties. Through this process, provisional tolerance daily intake (PTDI), provisional tolerance weekly intake (PTWI) and provisional tolerance monthly intake (PTMI) are decided.

From the standpoint that these are generally decided on the basis of NOAEL and LOAEL decided using toxicological assessment results, this is similar to the process for veterinary drugs, food additives and pesticides. However, for unintentional food contamination, such as the case with environmental contaminants, the term 'tolerable' is used instead of 'acceptable.'

Environmental contaminants have very strong toxicity unlike veterinary drugs, food additives and pesticides and the exposure is carried out unintentionally. Therefore, the traditional toxicological test has not been conducted on most of these substances.

In general, for fungal toxins, which are excreted rapidly and does not have strong accumulative property, PTDI, which is similar to ADI used for veterinary drugs, is decided. For heavy metals with high level of accumulation that display toxicity through long-term intake, PTWI is decided.

However, CODEX applies ALARA (as low as reasonably achievable) principle to genotoxic carcinogens (genotoxic and carcinogenic substances). In addition, for

substances with high bio-accumulation that have a very long half-life, such as dioxin, it is recommended to use PTMI as a toxicological standard.

3) Exposure Assessment

To decide estimated human exposure to contaminants, results of actual field survey are required. For exposure assessment, such information as exposure concentration, exposure frequency, exposure period and pathway, time of exposure, characteristics, size and composition of the exposed group and details concerning sensitive group must be provided.

Present or future exposure levels are predicted by combining levels of exposure to risk and exposed groups. Exposure assessment, as such, is carried out concurrently as hazard characterization and dose - response assessment and the results are combined in the last stage of risk characterization.

Livestock and humans are continuously exposed to environmental contaminants through air, water, soil and food (feed). Therefore, it is necessary to assess exposure amounts in relation to various contamination sources. Although the pathways of human exposure to environmental contaminants are diverse, CODEX takes into consideration exposure through foods only by eliminating exposure through air or drinking water in its exposure assessment.

In addition, when dietary exposure is decided using GEMS/ Food Regional Diets of FAO/ WHO and concentration of contaminants in each food item, and thus risk to human is identified through comparison with the set provisional tolerance intake, measures, such as ML establishment for foods that contribute significantly to dietary exposure or management of contamination sources, are taken.

In other words, for exposure assessment of environmental contaminants, assessment method different from that for veterinary drugs and food additives is used and the risk assessment, as such, is a very important process in selecting risk management plans. Assessment of exposure in foods is a process to decide tolerable level or risk management plan application by compositely examining results of survey on the level of contamination caused by contaminants in foods and intake of the foods on the basis of toxicological assessment results.

To set tolerable level in foods, CODEX generally conducts the following dietary exposure assessment.

4) Maximum Level (ML) Setting for Environmental Contaminants Using Dietary Exposure Assessment

ML setting for contaminants in foods is carried out through the four stages of exposure assessment. In stage 1, it is decided if ML setting is necessary considering current dietary exposure to contaminant and foods for which ML setting is necessary are selected. In stage 2, draft maximum level (draft ML) is decided.

In stage 3, dietary exposure through foods is assessed through ML application. In the last stage, substantial efficiency of ML setting, such as its impact on international trade, is examined. The procedures of ML setting for contaminants in relation to individual foods are expressed in the figure below.

❶ Stage 1

This is a process to select food items for which contaminant risk and ML setting is necessary. The following must be examined.

- Check if exposure to contaminant by dietary intake exceeds safe/ tolerable dietary exposure level

In this stage, total dietary exposure is calculated and it is examined as to whether or not the total dietary exposure is higher than PTWI or PTDI. The purpose of setting ML is to reduce the amount of contaminants in foods as much as possible. Exposure to contaminants must not exceed safe/ dietary exposure level calculated through toxicological assessment.

For this, toxicological data serve as a basis for the assessment conducted by Committee on Food Additives. If PTWI/ PTDI are not available for a substance to assess, JECFA examines all toxicological data decides the respective PTWI/ PTDI.

- Set food items or food groups for which ML setting is necessary

Although it is important to facilitate international trade, the key purpose of ML setting is to protect the health of consumers across the world. In general, it does not mean that exceeding ML causes health risks. For contaminants producing acute toxicity, it is necessary to set maximum tolerable concentration of the contaminants in foods in order to protect consumers' health.

However, most contaminants produce chronic toxicity over a long period of time. As for acceptance criteria for these substances, it is necessary to set them selectively for foods and food groups that significantly contribute to total dietary exposure of consumers only. The criteria set as such must be achievable through direct measures on contamination sources or GMP (good manufacture practice).

In this stage, foods that can cause risk are identified and draft ML is set for foods with large contribution to contamination as a means to reduce total dietary exposure to contaminants. To the process of food selection, the following four criteria are applied.

① When management action is applied to contamination sources, it must be ensured that ML is reached in all foods. The measures to eliminate or manage contamination sources or the measures to identify and categorize contaminated foods from those consumed by people must be recognizable as the measures with which to reduce concentration of contaminants in foods. It can take a long period of time for such an action to take effect. In addition, a process of consent by phase may be necessary until acceptance criteria are set.

② This targets foods or food groups that represent 10% or more of total dietary exposure in at least one region or specific group. For foods that belong to the same food group, but display different contamination levels or foods that requires risk management action of a different type, different acceptance criteria can be applied or the application can be exempted. In addition, for substances of which the main cause of exposure is not food intake, it is advised to set management criteria for contamination sources by country or region.

③ ML is decided targeting foods or food groups that are being traded internationally and contribute to total dietary exposure at significantly high

concentrations in at least two groups of GEMS/ Food Regional Diets classification. Or, it targets foods or food groups that represent 5% or more of total dietary exposure in one or more regions.

To satisfy these conditions, the foods must be traded between countries that have different dietary patterns and the importing countries must have evidences showing that total dietary exposure to specific contaminants increased to be higher than safe/ dietary exposure limit as a result of intake of the imported foods. In addition, evidences showing that consumers are exposed to contaminants in a level higher than the safe level as a result of unique dietary pattern of the importing country must be presented.

④ This targets foods of which the exposure does not exceed 5% of total dietary exposure in any groups specified in GEMS/ Food Regional Diets classification, but for which acceptance criteria play a very important role in food contaminant management or environmental monitoring (Ex.: Liver and kidney from edible parts of agricultural and animal-originated foods).

❷ Stage 2: Set draft ML by food item (group)

This is a stage to decide draft ML for foods selected in stage 1. Draft ML is decided at higher concentration levels from those detected from the foods selected in stage 1. It must be carefully evaluated whether or not the values can represent contamination concentrations of the foods and be measured with reliable analysis methods.

❸ Stage 3: Estimate dietary exposure by foods for which draft ML is set

This is the most important stage for deciding whether or not to accept draft ML set in stage 2. In stage 3, total dietary exposure is calculated using draft ML set for each food (food group) and food consumption amounts. In other words, the amount of exposure to contaminant through intake at draft ML is estimated by region assuming that a food holding draft ML is contaminated in draft ML.

For food consumption amounts used in this calculation, GEMS/ Food Regional Diets from FAO/ WHO is used. In Korea, it is more practicable to refer to food balance sheet and national health and nutrition examination survey. Although not all foods

are contaminated at draft ML, contamination level in a considerable number of foods would be similar to draft ML. When data are not sufficient, it is assumed that contamination concentration in 50% of foods for which draft ML is set is the same as draft ML.

Although this assumption may lead to exposure by foods to be assessed excessively, when the estimated dietary exposure calculated through this process is lower than PTWI/ PTDI, then the draft ML can be accepted. However, when dietary exposure is higher than PTWI/ PTDI, this means that draft ML has been set low. To examine this, an assessment to find out whether or not draft ML of a food can cause toxicological problems must also be conducted.

Through this process, CTC (calculated tolerable concentration) of foods for which draft ML is decided is calculated using regional dietary intake. This is to consider differences in food intake patterns by region. In other words, CTC is a concept introduced to decide the highest concentration of a contaminant in food that can be taken by consumers without going over PTWI/ PTDI of the contaminant as suggested by JECFA. This can be considered the same concept as TMDI.

● Calculating CTC for Individual Foods by Region

To decide CTC for individual foods in each region, a premise that dietary exposure by foods for which draft ML is suggested must be 80% or more of total dietary exposure must be satisfied. In addition, calculation must be carried out assuming that exposure by foods without draft ML 20% of exposure by all foods. Moreover, for estimation of exposure as such, it is assumed that the level of exposure through air or drinking water is extremely low.

In other words, CTC of a specific food with draft ML (CTC, g/day) = [PTWI (adult, μg/day) - exposure by all other foods (μg/day)] / intake of the respective food (g/day)

* Exposure by All Other Foods = Exposure by foods with draft ML - 20% of exposure by all foods (exposure by foods without draft ML)

- CTC of a region with the lowest CTC by food calculated in relation to individual foods with regional draft ML is selected. Then, the added concentration is compared against draft ML and the draft ML is adjusted accordingly. Under the condition that the adjusted draft ML does not exert serious economic effect, the lowest possible concentration is decided. The following two cases can be considered.

- In case CTC is higher than draft ML

  Draft Ml can be selected as ML. However, the tolerable level in this case must be at a concentration not causing risk to human health. In case ML is in a general contamination distribution range, it is considered that the ML would not exert economically serious effect.

- In case CTC is lower than draft ML

  CTC is selected as ML. This means that it is necessary to examine whether or not the proposed ML will exert adverse effect to economy and health. In foods that are contaminated at high concentrations, it is essentially required to set ML of a high concentration. ML must not be lower than detection level that can be analyzed using a method easily applicable in ordinary labs.

  However, in case health risk is possible even with a trace amount, a low detection level that is analyzed only with a more precise analysis technique can be considered as draft ML.

❹ Stage 4: Decide actual efficiency of ML setting

This is a stage to decide whether or not application of ML adjusted in stage 3 produces economic effect and enables safe food intake by people. The following two factors are taken into consideration.

- Economic effect of the proposed ML

  ML must not exert unnecessary economic or commercial burden on the WTO

member states. Countries where tolerable level is not set because of low dietary exposure to contaminants are subject to trade-related issues by reason of the health of people. In this case, the country must submit information concerning health-related risks to CCFAC and receive assessment.

- Guarantee that people in countries where ML is not set can take foods safely
  When calculating total dietary exposure of each region using the new ML set, the values must not exceed provisional tolerance intake in all regions. CODEX requires each country to monitor foods for which ML is set and these data are used to indicate how successfully the sources of contamination are being controlled. In addition, each country needs to administer monitoring also on foods for which ML is not set.

5) Method to Select Appropriate Data for Dietary Exposure Assessment

❶ Factors to be Considered in Food Contamination Data Selection

- Quality of data
  - Updated data
  - Analysis method must be verified and at a satisfactory quantitative level.
  - Data on analysis of individual samples
  - Samples must be taken according to sampling plan based on statistics.
  - Data must statistically represent the respective country or, if such is unattainable, a specific region of the country.
  - Sample count must be statistically sufficient so as to ensure statistical reliability.
  - In most cases, data must be about raw agricultural and animal-originated food materials.
  - When all of the conditions above are satisfied, distribution curve developed using the data can be used in estimating total dietary exposure for

contaminants or toxins.

- Using median has an advantage of eliminating the impact caused by the inclusion of samples that hold values below the limit of quantification.

● Values below Limit of Quantification

The level of contaminants in a considerably large number of samples is below the limit of quantification. In this case, limit of quantification 0 and the median of limit of quantification are used in exposure assessment. Processing of such data is sometimes dependent on food and contamination types.

● Intentional Data

Data collected as a result of the occurrence of special issues must not be used unless other data are not available. This is because, using these data, exposure amount and level can be assessed in excess of the actual exposure. FAO/ WHO's JECFA conducts dietary exposure assessment by eliminating such data.

▪ Past Data

Old data can be unclear about sample collection process, purpose and analysis method. Therefore, past data must not be used unless updated data are not available. If past data are inevitably used, the previously stated details must be specified.

▪ Sample Size

When using contamination distribution curve, the number of samples must have statical validity in order to obtain highly reliable values.

▪ Median and Mean

It is advisable to use median values. Median can be decided when values of each sample are available for use. Mean can be used only under specific assumptions.

❷ Data on Survey of Contaminants in Food, which are Used in Contamination Distribution Curve

▪ Individual Data

It is recommended to use individual data to secure satisfactory data quality. Using individual data, median, standard deviation and high statistical reliability can be obtained. However, in general, it is difficult to obtain such data.

▪ Group Data

In case individual data are not available and the number of samples below the limit of quantification is small, average values can be used. A distribution curve with high reliability can be obtained when concentration is expressed with log distribution. Although not all contaminants follow log distribution, most contaminants can be applied with it. Through log conversion, standard deviation and distribution curve, which are used by CCFAC in deciding risk management action, can be obtained.

▪ Food Intake Data

Information about individual food intake to represent each group is very important in building an international food model. The currently available information includes food balance sheet, national health and nutrition examination survey data and FAO's GEMS/ Food Regional Diet.

To identify overall food intake in Korea, it is advisable to use food balance sheet. If data on intake by food item and age group as well as intake by obese group are necessary, the data from Korea Health Industry Development Institute are recommended.

FAO's regional dietary intake data were prepared by WHO as part of the Global Environmental Monitoring System/Food Contamination Monitoring and Assessment Programme (GEMS/Food Regional Diet) project to assess the status/trend of food contamination by harmful chemicals and to assess their health risks.

In the beginning, it was based on agricultural products and categorized into five regions (Middle East, Far East, Africa, Latin America and Europe). However, in 1999, it was sub-divided into 13 regions (A - M). In the long term, the 13 regions can be applied in exposure assessment on food contaminants and toxicity. However,

the necessary data are insufficient at the moment.

<Example of Setting Tolerable Level of Lead in Foods>

(1) Stage 1

This is a process to identify foods for which it is necessary to set health risk by and ML of lead.

● Does exposure to lead through dietary intake exceed safe/ dietary exposure level?

▪ PTWI of Lead: In 1993, PTWI was assessed as 25㎍/㎏ bw based on a group with the highest sensitivity. In 2001, JECFA conducted a reassessment targeting ordinary adults, and thus decided the value as 214.3㎍/ day/ 60㎏ bw. When converted to PTWI, it is 25㎍/㎏ bw, which is the same as the assessment result in 1993.

▪ The concentration of lead contamination is decreasing as a result of management action on the contamination sources. However, exposure to it at a high concentration can cause health risk. As the gap between PTWI and estimated exposure is small, it is required to set draft ML in foods in order to reduce exposure to lead.

▪ Draft ML setting, as such, can lead to blocking the sale of foods contaminated in large quantities and encouraging each country to take measures to reduce contamination.

▪ The amount of exposure through air or water is extremely small, and thus can be ignored.

● Selecting foods for which tolerable level setting is necessary

▪ Dietary exposure for each food by region is decided using concentration of contaminants by food group and FAO/ WHO's food intake data.

▪ GEMS/ Food Regional Diet (1999, FAO/ WHO) for 13 regions is used.

- GEMS/ Food Regional Diet used to be classified into five regions. However, data from the recently proposed 13 regions have been used. Korea, together with Japan, belongs to group L.

▪ In case foods for which ML setting is necessary are selected according to criteria ① - ④ below, cereals, roots, tubers, vegetables, brassica, fruits, fish and wines are selected.

- Criterion ①: When management action is taken on the sources of contamination, the amount of contaminants in all foods must be less than draft ML according to the management action.
- Criterion ② : The selected food must be a food or a food group that represents 10% or more of total dietary exposure in at least one region or specific group.
- Criterion ③ : The food for which draft ML is to be decided must be a food or a food group that is being internationally traded and contributes to total dietary exposure with significantly high concentrations in at least two categories of GEMS/ Food Regional Diet classification or represents 5% or more of total dietary exposure in at least one region.

▪ A case in which 5% of total dietary exposure is not exceed in all groups, but ML has a very important function in management of contaminants in foods or environmental monitoring can be included.

▪ From agricultural and animal-originated foods, liver and kidney fall under this category. However, these are not distinguished from other meat products in FAO/ WHO's food intake data for 1999.

- Criteria ④ : Dietary exposure by foods for which draft ML is suggested must be 80% or more of total dietary exposure.

▪ Dietary exposure to lead through foods selected for lead is 84 - 94%.

(2) Stage 2: Setting draft ML for foods selected in stage 1

▪ Draft ML is decided using the range of concentration of contaminants by food in relation to the foods selected above.

<Table 5_1 Draft ML for Each Food>

Food	GEMS/Food 90th Percentile(mg/kg)	CCFAC comments since 1991	Draft ML (mg/kg)
Cereals	0.32	<0.005-0.26	0.5
Roots/tubers	0.08	<0.005-0.11	0.1
Vegetables	0.6	<0.005-2.4	2.0
Brassica	0.2	-	0.2
Fruit	0.13	<0.005-0.16	0.2
Fish	0.3	<0.005-0.82	0.8
Wine	-	0.06-0.15	0.2

▪ Contamination survey data submitted by each country (China, Iran, Japan, Singapore, Australia, Canada, Guatemala and Qatar) from 1990 to 1994 were used. Slight changes may apply when applicable data on contamination level are added.

(3) Stage 3: Estimating dietary exposure by foods for which draft ML is set

▪ This is a process to decide whether or not to accept draft ML. Dietary exposure by region is estimated assuming that the food holding draft ML is contaminated in the draft ML.

<Table 5_2 Dietary Exposure Estimates of Foods for which Potential Draft ML is Set by Region>

Region	A	B	C	D	E	F	G	H	I	J	K	L	M	PIWI
Exposure (μg/person /day)	202.1	698.8	476.6	420.8	470.3	384.5	382.5	270.3	242.0	264.8	235.1	514.6	483.8	214.3

▪ With an exception of region A, exposure is higher than PTWI. Therefore, it can be concluded that one or more draft MLs have been set highly.

▪ Exposure by All Other Foods = (Exposure by other foods for which draft ML is set) - (20% of exposure by all foods)

<Table 5_3 Exposure and Intake by Food in Group A Region>

Food	Dietary exposure(μg/day)	Intake (g/day)	Remarks
Cereals	7.7	255.3	PTWI : 214.3μg/ day, 60kg Total dietary exposure: 48.1μg/kg
Roots/tubers	19.6	392.1	
Vegetables	1.2	59.6	
Brassica	0.2	2.4	
Fruit	4.6	183.6	
Fish	1.9	18.6	
Wine	9.1	9.1	

□ Calculating CTC for the respective foods by region using the method above

Food	A	B	C	D	E	F	G	H	I	J	K	L	M	Lowest CTC
Cereals	0.66	0.32	0.31	0.35	0.44	0.46	0.38	0.43	0.47	0.41	0.6	0.4	0.46	0.31
Roots/tubers	0.46	0.74	2.7	0.66	0.55	0.65	1.6	1.8	0.49	0.51	1.0	1.3	0.86	0.46
Vegetables	2.7	0.31	0.65	0.7	0.49	0.83	0.84	1.8	2.1	1.8	2.0	0.53	0.5	0.31
Brassica	67	4.0	15	2.9	2.8	3.7	7.9	27	29	1570	38	2.7	8.6	2.7
Fruit	0.9	0.35	0.71	1.0	0.49	0.63	1.8	0.67	1.6	1.5	0.63	0.76	0.46	0.35
Fish	8.7	2.2	11	7.0	3.1	1.7	7.0	5.7	6.7	7.4	8.4	1.1	2.5	1.1
Wine	1.9	0.84	25	2.3	0.46	0.85	7.3	1.7	1.5	1.5	1.8	1.1	0.6	0.46

□ Setting ML through comparison between draft ML and CTC

Food	Draft ML (mg/kg)	CTC (mg/kg)	Proposed final ML (mg.kg)	CODEX MLs (mg/kg)	Remarks
Cereals	0.5	**0.31**	0.2	0.2	CTC reflected
Roots/tubers	**0.1**	0.46	0.1	-	Draft ML adopted
Vegetables	2.0	**0.31**	0.2	0.1	CTC reflected
Brassica	**0.2**	2.7	0.2	0.3	Draft ML adopted
Fruit	**0.2**	0.35	0.2	0.1	Draft ML adopted
Fish	**0.8**	1.13	0.5	0.2	Draft ML adopted
Wine	**0.2**	0.46	0.2	0.2	Draft ML adopted

▪ In case CTC is higher than draft ML: Although draft ML can be set, this must be done so as not to cause risk to human health. In case draft ML is within a

general contamination distribution range, serious economic impact is not caused.

▪ In case CTC is lower than ML: The level must be set as low as possible. For this case, CCFAC needs to discuss whether the proposed ML can exert economic and health impacts. In foods contaminated at high concentrations, it is necessary to set ML with a high concentration.

(4) Stage 4: Judging actual efficiency of the decided ML

● Calculating regional and total dietary exposure using the new criteria

▪ Assuming that individual foods are contaminated in ML, dietary exposure according to the contamination is calculated as of the following. The result indicates that PTWI is not exceeded in all regions.

<Table 5_4>

Region	A	B	C	D	E	F	G	H	I	J	K	L	M	PTWI
Exposure (㎍/ person/ day)	105.5	210.2	139	141.7	180.6	158.8	113.7	118.5	112.4	117.7	108.9	174.3	173.6	214.3

● Compare actual exposure to ML by country.

▪ Australia, China and Japan (as of 1990 - 1994): 10-170 ㎍/ person/ day

▪ Japan in the 90th Percentile: 50～260㎍/ person/ day

▪ Canada, Sweden, Denmark, U.K., Netherlands: 28～250㎍/ person/ day

● In conclusion, application of the decided ML can lead to protecting health of consumers in each region and is within contamination distribution range in each country. As it is not causing economic issues, it can be adopted as ML.

6) Risk Characterization

This is a process to set side effect occurrence predictions in a specific group. The value indicates the degree of actual or potential health risk. Risk characterization is to decide the possibility of causing health risk to a specific group considering uncertainty and variability based on the results of the previous hazard identification, hazard characterization and exposure assessment. Through this process, the possibility for humans to be affected by risk through exposure to hazards is estimated.

In CODEX, JECFA assesses risk of contaminants and toxins based on hazard characterization and exposure assessment results, and thus decides the degree of human exposure to environmental contaminants exceeding the limit intake specified by toxicological assessment or the degree of exposure to cause risk to humans.

Assessment results as such can contain technical means and scientific information suitable for risk management. In addition, CCFAC considers risk management plans, such as to set ML (draft) or to devise other legal measures based on the risk assessment results. The figure below is a schematic diagram of environmental containment contaminant risk assessment procedures.

Risk assessment on environmental contaminants is a series of composite operations carried out to decide risk management measures, which are used to reduce harmfulness of substances suspected of risk on humans. This is a process to decide toxicologically safe level based on toxicity assessment data, to decide actual human exposure based on contamination level and intake survey by each of various exposure pathways, such as food, air and water, and thus to decide the degree of risk exerted on humans through exposure to environmental contaminants by comparing the decided values with assessment results listed in toxicological data.

When the degree of risk on health caused by contaminants is decided through risk assessment, risk management measures are taken, such as to select foods for which ML setting is necessary and to set ML for the selected foods or to establish management criteria for the sources of contamination in order to reduce human exposure. to the contaminants. Below is an example of ML setting for melamine, which was administered in Korea.

In 2008, China experienced an incident of infants and toddlers dying.

Through a dynamics study, it was found that these children took powdered formulas manufactured by a specific company. In addition, it was found that these products were used as ingredients in foods distributed in Korea. At this, a number of government offices including the Ministry of Agriculture, Food and Rural Affairs and the Ministry of Food and Drug Safety collected suspected food items and conducted residue test.

Although the substance was not detected in foods and milk for infants and toddlers, a small amount was found in confectionary and breads. Therefore, the government decided that it was necessary to set MRL for foods. First, considering the incidence of infants and toddlers' death, MRL for infant and toddler food was set as 'no detection' using ALARA approach. For risk assessment on general foods, TDI was set as 0.05㎎/㎏ bw/day by applying safety factor of 10 to EU's EFSA 0.5㎎/㎏ bw/day.

In terms of food intake, a worst case scenario was assumed where the daily solid intake by a person weighing 60kg is 1,200g/day, and thus ML was set as 2.5mg/kg (ML = 0.05㎎/㎏ bw/day x 60㎏ person / 1.2㎎/㎏ person bw/day).

A considerable amount of exposure to contaminants is through foods. Therefore, countries across the world and international organizations are setting ML for foods in an attempt to reduce exposure to contaminants through foods.

Risk assessment on contaminants targets substances that can cause risk on human health. However, as toxicological data are insufficient for most contaminants and the types of exposure are diverse, ML cannot be decided in many cases using the same method for veterinary drugs or pesticides.

ML setting for agricultural and animal-originated foods is carried out by setting foods that contribute to dietary exposure through a process of dietary exposure assessment as contaminants affect various foods unlike in the case of veterinary drugs. Therefore, the level cannot be set singularly for agricultural and animal-originated foods.

However, ML is not set through the dietary exposure assessment for all contaminants. For contaminants of which contamination sources or contaminated foods are specified, assessment level is decided using separate assessment methods. For example, ML setting for aflatoxin M1, which is generated through aflatoxin B1 metabolism within the body, was carried out through the following assessment process.

The ML of aflatoxin M1 is not set based on toxicological data. It is set based on the amount of transition to milk in the form of aflatoxin M1 in feed. For example, in the U.S., 0.2 − 3.2% of aflatoxin B1 is metabolized into aflatoxin M1, and thus is transferred to milk. In addition, the level is set as 0.5ppb assuming that the level of aflatoxin B1 is 20ppb, feed intake by cow is 16kg/day and milk production per day is 20L. In other words, when transition rate is 0.2%, content in milk is 0.0032ppb (20㎍/㎏ x 16㎏ x 0.2% / 20L) and, when the rate is 3.2%, the content is estimated to be 0.512ppb (20㎍/㎏ x 16㎏ x 3.2% / 20L). Therefore, ML in milk is decided as 0.5ppb.

In addition, as of dioxin compounds, when a number of compounds of the same type are concurrently exposed to, relative toxic equivalents (TEQ) are decided for each substance based on toxicity of a substance that has the highest toxicity, and thus the TEQs are applied in deciding toxicologically safe level. A number of reports have been made on the results of toxicity assessment on 2, 3, 7 and 8-TCDD, which has the highest toxicity.

However, reports on toxicity assessment results about other analogous compounds are extremely insufficient. Therefore, toxicologically safe level for dioxin compounds (PTDI) is set on the basis of toxicological assessment results and results of studies on bio-dynamics of 2, 3, 7 and 8-TCDD in lab animals.

As a system slightly different from that for veterinary drugs or pesticides is applied and setting tolerable levels in foods requires contamination survey in various foods groups in addition to toxicological study reports. Accordingly, the process takes a very long period of time.

Most environmental contaminants are highly toxic and lipotropic. Therefore, their accumulative property in agricultural and animal-originated foods is high. As a result, deriving risk management plans through risk assessment on these substances has

become a very important issue. In Korea, it is also necessary to establish risk management plans as such by introducing risk assessment methods for these substances.**[Attachment]**

Terms and Definitions

○ Acute reference dose (ARfD)

This is a daily acute reference dose. ARfD is an amount of a substance of which risk to health is not detected within 24 hours from food intake.

○ Exposure assesment

This is a process to quantitatively or qualitatively estimate the level of human body exposure to specific hazards through intake of agricultural and animal-originated foods.

○ Exposure scenario

This refers to a collection of facts, assumptions and inferences about the method and status of exposure occurrence that is helpful in estimating or quantifying exposure for exposure assessment.

○ Margin of exposure (MOE)

MOE is calculated by dividing POD (point of departure) value (NOAEL or BMDL) with a value for estimated dose/ exposure level.

○ Monte Carlo

A stochastic system tool used to supplement uncertainty of exposure assessment

○ No observed adverse effect level (NOAEL)

Maximum dose of a chemical of which no adverse effect is observed in animal toxicity test

○ No observed effect level (NOEL)

Maximum does of a chemical of which no effect is observed in animal toxicity test

○ Cancer risk

Cancer risk can be defined as the possibility of cancer outbreak during the life cycle of a person according to exposure to carcinogenic substances. The risk of cancer occurrence is decided with carcinogenicity and exposure information of the substance concerned. In particular, carcinogenic risk is calculated through multiplication with cancer slope factor specific to exposure pathway.

○ Uncertainty factor (UF)

When predicting effects on human using lab animal data, this factor is used for adjustment considering differences between species, differences between individuals, synergistic effect and various uncertain sources of generation caused by different pathways.

○ Benchmark dose (BMD)

First introduced by Crump (1984), BMD is based on dose - response modeling. It is defined with lower confidence limit for effective doses related with the effects that are known to a degree (response increased by 5% or 10%). In other words, BMD is a confidence limit for doses that trigger adverse effects in the fraction of lab animals (mostly 5% or 10%). based on a graph describing confidence limit, BMD is used to calculate the desired response rate (BMR, 5% or 10%).

○ Food balance sheet

According to FAO's recommendation, food balance sheet has been prepared since 1962. Food balance sheet lists the status of food supply to the people together with food and nutrient supply per person per day. Therefore, it is widely used as basic data for food supply policy setting and in studies to improve people's nutrition intake and diet. It is also available for comparison with data from various countries across the world. At present, food balance sheet is distributed by Korea Rural Economic Institute.

○ Margin of safety (MOS)

MOS is set by dividing HBGV, such as acceptable daily intake (ADI, TDI or ARfD), with LADD, the chemical exposure or intake.

○ Good agriculture practices (GAP)

To apply environmental, economic and social knowledge in order to ensure safety and sanitation for agricultural products in the course of production and the follow-up processes

○ Good veterinary drug practices (GVDP)

All contents relating to correct use of veterinary drugs for safety of agricultural and animal-originated foods

○ Health based guidance value (HBGV)

○ Risk Analysis

This is a series of processes to establish management plans and measures to protect the health of livestock product consumers and to reduce residues or contamination of harmful chemicals in agricultural and animal-originated foods based on the results of scientifically conducted risk assessment, and thus to exchange opinions about the plans and measures with consumers and other related persons. Risk analysis is comprised of risk assessment, risk management and risk information exchange operations.

○ Hazard

Chemical, physical or biological factors in and status of agricultural and animal-originated foods that have potential adverse effects on human health

○ Risk assessment

This is a process to scientifically predict and assess the possibility of adverse effect on human health and the degree of impact caused by exposure to hazards existing in agricultural and animal-originated foods. Risk assessment is comprised of hazard identification, hazard characterization, exposure assessment and risk characterization operations.

○ Hazard identification

This is a process to scientifically check toxicity or harmfulness of hazards in human body. Risk-related information, such as test and research outcomes, dynamics study results, information on relevance between chemical structure and action and information about target organs, is comprehensively used in identifying harmfulness of hazards in agricultural and animal-originated foods.

○ Hazard characterization

A process to quantitatively or qualitatively calculate impact of hazards on human health as acceptable human exposure, etc. through dose - response assessment of the hazards

○ Risk characterization

A process to decide the level of human exposure to identified hazards and the degree of risk on human health and to suggest appropriate safety management criteria or safety management goals for agricultural and animal-originated foods

○ Limit of quantification (LOQ)

Minimum amount of chemical that can be quantified using reliable analysis technique

○ Maximum residue level (MRL)

Maximum concentration of substances remaining in foods or animal feeds as a result of the use of veterinary drugs or pesticides. MRL is expressed with mg/kg and ㎍/ ㎏.

○ Lifetime average daily dose (LADD)

An average of exposure amount through life cycle of an individual considering frequency, period and intensity of exposures

○ Cohort study

This is a study to continuously track down a group holding hazards and to check whether or not the hazards produce results. In dynamics study, Cohort studies generally refer to forward-looking comparative studies.

○ Quantitative structure - activity relationship (QSAR)

QSAR means quantitative correlation between chemical property and activity. It is used in relation to biological or toxicological activity models. This is a tool to estimate toxicity of a substance by assuming that, when physicochemical characteristics of chemicals are similar, their toxicological properties are also similar.

[Attachment 2]

Agricultural Products Risk Assessment Enforcement Guidelines

(Ministry of Agriculture, Food and Rural Affairs Announcement 2011-187, established on Nov. 23, 2011)

Article 1 (Purpose) The purpose of this Announcement is to define details necessary in risk assessment in order to ensure scientific and systematic implementation of risk assessment on agricultural products (to be referred to as 'risk assessment' hereinafter) according to Article 14-6 of Agricultural Products Quality Control Act (to be referred to as 'the Act' hereinafter), Article 21 of the Enforcement Decree of the same Act (to be referred to as 'the Decree' hereinafter) and Article 21-8 of the Enforcement Regulations of the same Act (to be referred to as 'the Regulations' hereinafter).

Article 2 (Definitions) The terms used in these Guidelines shall be defined as follows:

1. The term 'hazard' refers to chemical, physical, microbiological and environmental elements in agricultural products that have potential risk for human health.
2. The term 'risk assessment' refers to a series of processes to scientifically predict harmful impact and probability of such impact to occur when human body is exposed to hazards existing in agricultural products. Risk assessment is comprised of hazard identification, hazard characterization, exposure assessment and risk characterization.
3. The term 'hazard identification' refers to a process to scientifically check potential characteristics of hazards to produce toxicity in human body.
4. The term 'hazard characterization' refers to a process to quantitatively or qualitatively calculate the acceptable amount of human body exposure to hazards through dose - response assessment of hazards.
5. The term 'exposure assessment' refers to a process to quantitatively or qualitatively estimate the level at which human body is exposed to specific hazards through the intake of agricultural products.
6. The term 'risk characterization' refers to a process to decide the level of human exposure to identified hazards and the degree of harmfulness exerted by identified hazards on human health, and thus to suggest appropriate safety management criteria or safety management goals in relation to agricultural products cultivation environments, such as farmland and materials used.

7. The term 'acceptable amount of human exposure' refers to an amount of hazard flown into human body through agricultural products and environment that is not recognized to produce risk under the current scientific level. According to hazard characteristics, this refers to ADI, TDI and weekly intake.
8. The term 'appropriate safety management criteria' refers to management criteria set to prevent risk on human body that can be caused by inflow of hazards to human body through agricultural products and environment. This refers to safety criteria in production stage (up to forwarding), MRL of hazard in agricultural products, acceptable microbial level or forwarding delay period.

Article 3 (Agricultural Products and Hazards Subject to Risk Assessment) Agricultural products and hazards subject to risk assessment shall be as listed in Subparagraph 1 and 2, Paragraph 2, Article 21-8 of the Regulations.

Article 4 (Establishing Risk Assessment Plan) ① Agricultural, Food and Rural Affairs Minister shall establish risk assessment plan including agricultural products and hazards subject to risk assessment and purpose, entity and period of risk assessment.

② In case there are a large number of agricultural products and hazards subject to risk assessment pursuant to Paragraph 1, Agricultural, Food and Rural Affairs Minister can decide the order of priority considering degree of risk and urgency.

③ In the event such measures as disposal, conversion of use and forwarding delay are taken in relation to ingredients or properties of agricultural products for which prompt preventative action is necessary to national health protection according to Paragraph 1, Article 14-6 of the Act, Paragraph 3, Article 21 of the Decree and Article 21-8 of the Regulations, risk assessment can be requested preferentially notwithstanding the provisions in Paragraph 1 and 2 above.

Article 5 (Risk Assessment Procedures) ① Risk assessment is carried out on the impact of agricultural products on human health through the process of hazard identification, hazard characterization, exposure assessment and risk characterization.

② According to Paragraph 1, Article 14-6 of the Act, an organization requested of risk assessment by Agricultural, Food and Rural Affairs Minister can omit some procedures or apply risk assessment technologies developed and verified domestically and internationally in the event current scientific and technological standard and data are not sufficient, and thus assessment through all procedures is difficult to achieve.

③ According to Paragraph 1, Article 14-6 of the Act, an organization requested of risk assessment by Agricultural, Food and Rural Affairs Minister can collect opinions from the related experts when necessary in risk assessment and shall document and manage risk assessment process and risk assessment results.

④ Risk assessment report shall include characteristics of agricultural products and hazards subject to assessment, method and ground of risk assessment, assessment results by assessment element, such as hazard identification, hazard characterization and exposure assessment and recommendations for risk management plans. It shall also specify scientific or statistical data used in the assessment together with limitations in current technological level, uncertainties and assumptions that may affect the results of risk assessment.

⑤ When risk assessment report is completed, Agricultural, Food and Rural Affairs Minister shall submit the report for deliberation by Agricultural Products Quality Management Review Board Safety Subcommittee (to be referred to as 'Subcommittee' hereinafter) according to Paragraph 7, Article 3 of the Act and Article 7 of the Decree. However, when risk assessment is urgent, the deliberation can be postponed to after the assessment.

Article 6 (Risk Assessment Method) ① Risk assessment method is as follows:

1. Check types of hazards that can be taken through agricultural products, assess types and characteristics of hazards on human health and the related clinical study and forecast results and identify population groups affected sensitively by harmfulness of the hazards concerned.
2. Calculate acceptable human exposure amounts, such as ADI, by calibrating uncertainties in animal test results.
3. Quantitatively or qualitatively calculate amounts or levels of hazards to which humans can be exposed through agricultural products.
4. Quantitatively or qualitatively predict impact on health caused by hazards and the intake of agricultural products containing such hazards, acceptable human exposure to the hazards and products and the degree and frequency of risks caused by environment other than the intake of agricultural products. Suggest an appropriate safety management standard by compositely considering the prediction results and ensure scientifically valid risk management.

② In case the current science and technology level or data are insufficient or prompt risk assessment is required, the Agriculture, Food and Rural Affairs Minister can request risk assessment according to each of the following Subparagraph.

1. Comply with or apply decisions and results of hazard identification and hazard

characterization carried out by international risk assessment organizations or reliable domestic and foreign risk assessment agencies.

2. In case hazard characterization is difficult, estimate acceptable human exposure based on the limited hazard identification result or available scientific models.
3. In case risk characterization is difficult, predict the degree of risk based on hazard identification and exposure assessment results.
4. In case such risk as death occurred as a result of agricultural product intake, check the degree of risk.
5. In case exposure assessment data are insufficient or not available, conduct exposure assessment based on available scientific models.
6. In case the possibility of exposure or risk is considered large for specific groups, conduct risk assessment targeting sensitive and high risk groups, such as children, pregnant women and elders.

③ Detailed risk assessment methods for specific hazards can be decided by subcommittees according to types and characteristics of the hazards.

Article 7 (Requesting Risk Assessment to External Organizations) ① When requesting risk assessment to external organizations, such as producer groups and consumer groups, the Agriculture, Food and Rural Affairs Minister, when considered necessary, can convene subcommittees according to Article 7 of the Decree and deliberate on conformance of the request with Subparagraph 1 and Subparagraph 2, Article 21-8 of the Regulations.

② For deliberation by subcommittee according to provisions in Paragraph 1 above, the Agriculture, Food and Rural Affairs Minister can request the following data to external organizations, such as producer groups and consumer groups, to which risk assessment was requested.

1. Objective evidentiary data on the possibility of risk occurrence or hazard
2. Types of hazards and the target agricultural products and level of hazard detection
3. Regulatory status of and risk assessment results from international or foreign organizations, such as CODEX
4. Other data necessary in risk assessment

Article 8 (Announcement of the Results of Risk Assessment) According to Paragraph 2, Article 21 of the Decree, the Agriculture, Food and Rural Affairs Minister shall announce the results of risk assessment by posting them in Agricultural Products Safety Information System and the website of the Ministry of Agriculture, Food and Rural Affairs.

Addenda <No. 2011-187, Nov. 23, 2011>

Article (Enforcement Date) This Announcement shall enter into force as of the day of announcement.

Article 2 (Time Limit for Re-examination) This Announcement shall be reexamined by November 22, 2014 according to Subparagraph 2, Paragraph 3, Article 7 of the Regulations on the Issue and Management of Instructions and Standing Operating Procedure (Presidential Instructions No. 248).

[Attachment 3]

Livestock Products Risk Assessment Method, Criteria and Procedures

National Veterinary Research & Quarantine Service Announcement 2010- 10 (established on Nov. 26, 2010)

Animal, Plant and Fisheries Quarantine and Inspection Agency Announcement No. 2011- 44 (established on Jun. 15, 2011)

Ministry of Food and Drug Safety Announcement 2013- 49 (established on Apr. 5, 2013)

Article 1 (Purpose) The purpose of these Guidelines is to define details concerning risk assessment method, procedures and announcement for scientific, objective and transparent implementation of risk assessment on livestock products (to be referred to as 'risk assessment' hereinafter) according to Article 33-2 of the Livestock Products Sanitary Control Act (to be referred to as 'the Act' hereinafter) and Article 26-4 of the Enforcement Decree of the same Act (to be referred to as 'the Decree' hereinafter).

Article 2 (Definitions) The terms used in these Guidelines shall be defined as follows:

1. The term 'hazard' refers to chemical, microbiological and physical elements in animal products that have potential risk for human health.
2. The term 'risk assessment' refers to a series of processes to scientifically predict harmful impact and probability of such impact to occur when human body is exposed to hazards existing in animal products. Risk assessment is comprised of hazard identification, hazard characterization, exposure assessment and risk characterization.
3. The term 'hazard identification' refers to a process to scientifically check potential characteristics of hazards to produce toxicity in human body.
4. The term 'hazard characterization' refers to a process to quantitatively or qualitatively calculate the acceptable amount of human body exposure to hazards through dose - response assessment of hazards.
5. The term 'exposure assessment' refers to a process to quantitatively or qualitatively estimate the level of human exposure to specific hazards through intake of livestock products.
6. The term 'risk characterization' refers to a process to check the degree of human exposure to the identified hazard and the degree of impact caused by the hazard on human health and to suggest appropriate safety management standard or safety management goals for livestock products.
7. The term 'acceptable human exposure' refers to an amount of hazard of which it is considered that risk is not produced by the current science level when the hazard flows into human body through livestock products and environment. According to characteristics of hazard, this refers to acceptable daily intake, tolerable daily intake

and weekly intake amount.

8. The term 'appropriate safety management standard' refers to management standard set to prevent human risk caused by hazards flowing into human body through livestock products and environment. This refers to management standard for maximum residue of hazard in livestock products and acceptable microorganism level or distribution temperature.

Article 3 (Risk Assessment Target and Hazard as Assessment Target) For livestock products and hazard subject to risk assessment, provisions in Subparagraph 1 and Subparagraph 2, Paragraph 1, Article 26 of the Decree shall be observed.

Article 4 (Establishing Risk Assesment Plan) ① The Food and Drug Safety Minister (to be referred to as 'the Minister' hereinafter) shall establish plans for risk assessment including livestock products and hazards for which risk assessment is to be conducted in relation to substances that are considered risk to human health as well as purpose, entity and period of assessment, and thus implement the assessment.

② In case a large number of livestock products are subject to risk assessment according to provisions in Paragraph 1, the Minister can assess them by deciding order or priority considering the degree of risk and urgency.

③ In case sale or processing, packaging, use, import, storage, transport or display for the purpose of sale is temporarily banned for livestock products of which prompt preventative action is necessary to protect people's health according to provisions in Paragraph 2, Article 33-2 of the Act, the Minister, notwithstanding the provisions in Paragraph 1 and Paragraph 2, can preferentially conduct risk assessment.

Article 5 (Risk Assessment Procedures) ① Risk assessment is carried out through the procedures of hazard identification, hazard characterization, exposure assessment and risk characterization and it is aimed at deciding the impact the respective livestock products exert on health.

② In case currently science and technology level and data are not sufficient, and thus it is difficult to conduct the assessment through all procedures, the Minister can omit some procedures or apply a new domestically or internationally developed risk assessment technology.

③ If necessary in the course of risk assessment, the Minister can listen to opinions of the related experts and shall document the risk assessment process and risk assessment report for management.

④ Risk assessment report shall include characteristics of the target livestock products and hazards, risk assessment method and ground, results of each assessment element, such as hazard identification, hazard characterization and exposure assessment and recommendations for risk management plans. It shall also specify scientific or statistical data used in the assessment together with limitations in currently available technology level, uncertainties and assumptions that may affect the results of risk assessment.

⑤ When risk assessment report is completed, Agricultural, the Minister shall submit the report for deliberation by Committee. However, when risk assessment is urgent, the

deliberation can be postponed to after the assessment.

Article 6 (Risk Assessment Method) ① Risk assessment method is as follows:

1. Check types of hazards that can be taken through livestock products and assess types and characteristics of hazards on human health and the related clinical study and forecast results.
2. Calculate acceptable human exposure amounts, such as ADI, by calibrating uncertainties in animal test results.
3. Quantitatively or qualitatively calculate amounts or levels of hazards to which humans can be exposed through livestock products.
4. Quantitatively or qualitatively predict impact on health caused by hazards and the intake of livestock products containing such hazards, acceptable human exposure to the hazards and products and the degree and frequency of risks caused by environment other than the intake foods. Suggest an appropriate safety management standard by compositely considering the prediction results and ensure scientifically valid risk management.

② In case the current science and technology level or data are insufficient or prompt risk assessment is required, the Minister can request risk assessment according to each of the following Subparagraph.

1. Comply with or apply decisions and results of hazard identification and hazard characterization carried out by international risk assessment organizations or reliable domestic and foreign risk assessment agencies.
2. In case hazard characterization is difficult, estimate acceptable human exposure based on the limited hazard identification result or available scientific models.
3. In case risk characterization is difficult, predict the degree of risk based on hazard identification and exposure assessment results.
4. In case such risk as death occurred as a result of livestock product intake, check the degree of risk.
5. In case exposure assessment data are insufficient or not available, conduct exposure assessment based on available scientific models.
6. In case the possibility of exposure or risk is considered large for specific groups, conduct risk assessment targeting sensitive and high risk groups, such as children, pregnant women and elders.

③ For detailed risk assessment method for specific hazards, decisions made by the Committee according to types and characteristics of hazards can be followed.

Article 7 (Requesting Risk Assessment to External Organizations) ① When requesting risk assessment to external organizations, such as producer groups and consumer groups, the Minister, when considered necessary, can convene Subcommittees of Livestock Product Sanitation Review Committee (to be referred to as 'the Committee') according to Article 3-2 of the Act and deliberate on conformance of the request with Item C, Subparagraph 1, Paragraph 1, Article 26-4 of the Decree.

② For deliberation by the Committee according to provisions in Paragraph 1 above, the Minister can request the following data to external organizations, such as producer groups and consumer groups, to which risk assessment was requested.

1. Objective evidentiary data on the possibility of risk occurrence or hazard
2. Types of hazards and the target agricultural products and level of hazard detection
3. Regulatory status of and risk assessment results from international or foreign organizations, such as CODEX
4. Other data necessary in risk assessment

Article 8 (Announcement of the Results of Risk Assessment) ① The Minister shall decide the announcement of the result of risk assessment and the scope of announcement following deliberation on the risk assessment report by the Committee.

② In the event risk assessment result announcement is decided according to Paragraph 1, the Minister shall announce the result to the press or through the Ministry of Food and Drug Safety website.

Addenda <No. 2013-49, Apr. 5, 2013>

Article 1 (Enforcement Date) This Announcement shall enter into force as of the day of announcement

Article 2 (Time Limit for Re-examination) This Announcement shall be reexamined by June 14, 2014 according to Subparagraph 2, Paragraph 3, Article 7 of the Regulations on the Issue and Management of Instructions and Standing Operating Procedure (Presidential Instructions No. 248).

[Attachment 4]

Guidelines on Risk Assessment Target Substance Selection Criteria, Procedures and Method

[Enforced on Sep. 7, 2012] [National Institute of Environmental Research Announcement No. 2012-30, partially amended on Sep. 7, 2012]

Article 1 (Purpose) The purpose of this Announcement is to define necessary prescriptions for risk assessment target substance selection criteria, procedures and method according to provisions in Article 18 of Toxic Chemicals Control Act (to be referred to as 'the Act' hereinafter) and Paragraph 2, Article 14 of the Enforcement Regulations of the same Act (to be referred to as 'the Regulations' hereinafter).

Article 2 (Definition) The terms used in this Announcement shall be defined as follows:

1. The term 'risk assessment' refers to a process to systematically examine and assess exposure and toxicity information, and thus to predict the impact of chemicals on human body and ecosystem.
2. The term 'hazard characterization' refers to a process to verify harmful impact exerted on human body or ecosystem by chemicals based on study data about chemical toxicity and mechanisms and also to validate certainty of the evidences.
3. The term 'exposure assessment' refers to a process to estimate the level of exposure of human body or other receptors to chemicals based on quantitative and qualitative analysis data about the chemicals in environment.
4. The term 'exposure pathway' refers to a transfer medium and the pathway through which human body or ecosystem is exposed to chemicals generated from environmental sources.
5. The term 'bio-marker' refers to chemicals and metabolites of the chemicals measured inside a body in relation to chemical exposure and substances generated through reaction between the chemicals and specific molecules or cells.
6. The term 'internal dose' refers to the amount of exposed chemicals absorbed into living body.
7. The term 'dose - response assessment' refers to a process to verify correlation between a level of chemical exposure and its impact on human and ecosystem.
8. The term 'risk characterization' refers to a process to estimate quantitative level of risk caused by exposure to chemicals based on the results of exposure - reaction assessment

and to suggest uncertainty of the estimated level.

9. The term 'receptor' refers to individuals or species from the ecosystem that can be affected by chemicals.
10. The term 'bioconcentration' refers to a relative increase of the concentration of a chemical in a biological tissue in comparison to its concentration in an environmental medium. Bioconcentration factor is the concentration ratio
11. The term 'biomagnification' refers to the concentration of a substance increasing gradually towards predators in the food chain of ecosystem.
12. The term 'carcinogenic' refers to a property of a chemical to cause cancer or increase cancer occurrence.
13. The term 'threshold' refers to a dose where it is expected that harmful impact would not be generated at the level or below.
14. The term 'no observed adverse effect level/ no observed effect concentration (to be referred to as 'NOAEL' or 'NOEC' hereinafter)' refers to an exposure amount or a concentration that causes no significant increase both statistically and biologically in the frequency or severity of adverse effect between a group exposed to chemicals, such as in a dose - response test for chronic toxicity, and a control group. However, when certain effect occurs with such an exposure amount and it has no direct relevance with any specific harmfulness, it is not regarded as an adverse effect.
15. The term 'lowest observed adverse effect level/ lowest observed effect concentration (to be referred to as 'LOAEL' or 'LOEC' hereinafter)' refers to the minimum exposure amount with which statistically or biologically significant increase in the frequency or severity of adverse effects is observed between a group exposed to chemicals, such as in dose - response test, and a control group.
16. The term 'benchmark dose (to be referred to as 'BMD hereinafter)' refers to an estimate of exposure amount associated with a case in which toxicity impact increases specifically, such as by 5% or 10% than control group. In addition, the term 'benchmark dose lower confidence (to be referred to as 'BMDL' hereinafter)' refers to the lowest value of BMD estimated from a dose - response model within the confidence interval.
17. The term 'tumorigenic dose' refers to daily exposure for life cycle that is associated with a case in which the frequency of tumor occurrence as a result of exposure to chemicals displays a significant increase by 5, 10 or 25%.
18. The term 'margin of exposure (to be referred to as 'MOE' hereinafter)' refers to the ratio between exposure and NOAEL, BMD or excessive tumorigenic dose, which is used to quantitatively express risk level.
19. The term 'reference dose (to be referred to as 'RfD' hereinafter)' refers to an exposure

with which harmful impact is not produced when the associated chemicals flow into human body through foods and environment.

20. The term 'extrapolation' refers to a process to estimate the risk level of chemicals in low-concentration level, which cannot be observed, from a range in which observation is possible.
21. The term 'uncertainty factor' or 'assessment factor' refers to a temporarily calibrated value for extrapolation of results on animal test about chemical toxicity to human body or for application to sensitive targets.
22. The term 'predicted no effect concentration (to be referred to as 'PNEC' hereinafter)' refers to an environmental concentration that is predicted not to cause any harmful impacts on organisms living in the ecosystem other than humans.
23. The term 'predicted environment concentration (to be referred to as 'PEC' hereinafter)' refers to an environmental concentration to which it is predicted that organisms other than humans living in the ecosystem are exposed.
24. The term 'endpoint' refers to a quantitative and qualitative expression of a specific toxicity relating to the risk of a chemical.
25. The term 'hazard quotient' refers to a value used to express risk level of chemicals that is calculated by dividing human exposure with RfD or PEC by PNEC.
26. For other definitions, follow 'Regulations on Hazard Examination of Chemicals (National Institute of Environmental Research Announcement No. 2005-19, Jan. 6, 2006)' shall be followed.

Article 3 (Criteria for Risk Assessment Target Substance Selection) Substances for risk assessment shall be selected according to the following criteria.

1. Of chemicals produced and distributed by 1,000 tons or more, those scientifically proven to have harmfulness on humans and environment as a result of chemical distribution volume survey pursuant to provisions in Article 17 of the Act and Article 12 of the Regulations
2. Chemicals that build up in humans and environment over a long period of time or can cause serious exposure as a result of the use, persistence, biological concentration and biological magnification of the chemicals
3. Chemicals to which sensitive targets, such as groups subject to a large scale of exposure or serious risk, are exposed
4. Chemicals of international concern that are related with international conventions
5. Chemicals with sufficient data on risk available

Article 4 (Risk Assessment Procedures) In assessing risk level of chemicals on humans and environment, each of the following shall be taken into consideration.

1. Hazard identification
2. Exposure - response assessment
3. Exposure assessment
4. Risk characterization

Article 5 (Hazard Identification) ① Toxicity items to check harmfulness of chemicals on humans and ecosystem are as listed in Appendix Table 1. If other toxicity information is available, the respective items can be included.

② If appropriate human data, such as dynamics study results, are available in assessing harmfulness of chemicals on human health, the data must be reviewed in preference to animal test data. In this case, animal toxicity test data and in vitro toxicity test data are used to supplement insufficient evidences obtained from human study results.

③ Each of the following shall be taken into consideration in assessing harmfulness of chemicals on ecosystem.

1. Basic characteristics of ecosystem in assessment target area
2. Receptor that reacts most sensitively to chemicals and can be used as an indicator of ecotoxicity
3. Quantitative and qualitative endpoints, such as EC50 and NOEC for mortality and reproductive impact
4. Information about bio-accumulative property of chemicals

④ When assessing harmfulness of chemicals using existing animal test data, each of the following data shall be presented (Appendix Table 2).

1. Whether or not exposure to chemical exerts harmful impact on human body and environment
2. Exposure level and environmental conditions under which identified hazard is displayed
3. Distinct endpoint at which most significant exposure - response relationship is displayed

Article 6 (Exposure - Response Assessment) ① In case exposure - response assessment data are available sufficiently, the data can be quoted.

② In case valid exposure - response information is not available and it is necessary to estimate a new exposure - response relationship using animal toxicity test data or dynamics

data, estimation shall be carried out according to procedures set forth in Annexed Table 3 and each of the following shall be taken into consideration.

1. Exposure - response assessment shall be conducted separately for impacts with and without thresholds according to exposure as long as proven scientific grounds are not available.
2. For toxicity items of which toxicity is not observed, such as chronic toxicity, reproductive and development toxicity and nervous and behavioral abnormalities, at an exposure level or lower, it shall be assumed that such toxicity items cause health impacts with thresholds.
3. For toxicity items that display potentials for risk, such as carcinogenicity caused by mutableness and genotoxicity at all exposure levels, it is assumed that such toxicity items cause health impacts without thresholds.

③ For non-carcinogenicity assessment, NOAEL or BMDL, which is estimated as thresholds, can be calculated. In this case, the calculation shall be carried out using the method specified in Annexed Table 4.

④ For carcinogenicity assessment for which no threshold is assumed, BMDL or carcinogenic exposure dose exceeding 1 - 25% of observation range in an exposure - response model derived from animal tests or human dynamics study data is estimated.

⑤ In case there are no separate evidences about nonlinear relationship in an exposure - response model, carcinogenic potentials can be estimated through low-dose extrapolation (Annexed Table 5).

⑥ RfD can be decided through extrapolation from a high exposure dose for which toxicity has been observed to low exposure dose. In this case, the applied uncertainty factor shall be specified.

⑦ PNEC is derived from exposure - response model from ecotoxicity data. Calculation shall be carried out according to method in Annexed Table 6.

Article 7 (Exposure Assessment) ① Human or receptor exposure dose shall be estimated considering exposure pathways from discharge source data or concentration measured in environment.

② Methods listed in the following Subparagraph can be used in estimating exposure dose of chemicals in environment.

1. Directly measure dose in environmental medium
2. Estimate dose according to scenarios, such as behavioral model in environment
3. Use exposure-related bio-markers

③ The result of exposure estimation according to the scenario in 2. of Paragraph 2 and the

directly measured exposure can be used as mutually supplementing data and appropriateness, characteristics and variability in use of the behavior model are described in detail. The measurements can be used for model verification.

④ As for concentration in environment, detection limit and detection frequency as well as the parameters of sample count, average value (arithmetic and geometric), deviation, upper limit and lower limit shall be suggested.

⑤ Assumptions used to predict human exposure shall be as accurate and reasonable as possible. If expose - response assessment has been conducted with net dose in human body, the dose of the respective format shall be displayed.

⑥ In case measurements of exposure intensity, exposure rate, exposure period and exposure frequency for human exposure calculation are not available, the values in Annexed Table 7 are used as exposure factors.

⑦ For concentration in environment to which receptors in the ecosystem are exposed, PEC is calculated as a single estimate by exposure pathway or as exposure distribution (Annexed Table 8).

Article 8 (Hazard Characterization) ① The degree of risk according to exposure to chemicals is calculated based on exposure - response assessment and exposure assessment results.

② When there are more than one risk, the level of risk of the targe group can be displayed as the sum of risks assuming additivity. For this, the following shall be satisfied.

1. Each risk to be sufficiently small
2. Each impact to be independent from one another
3. Target organ and toxic mechanism of each impact to be the same and each impact to display similar exposure - response model

③ Risk of noncarcinogenic impact assuming threshold can be displayed as follows:

1. MOE, the ratio of NOAEL or BMDL to exposure level
2. Risk factor, the ratio of RfD to exposure level
3. Stochastic distribution of MOE or risk factor

④ Carcinogenic risk assuming threshold can be expressed with carcinogenic dose with exposure excessive by 1, 5, 10 and 25%, MOE, the ratio of BMDL to human exposure, or excessive carcinogenic probability of the target group according to the stage of linear extrapolation in relation to low dose exposure.

⑤ In case risk factor is larger or likely to be larger than 1, it is considered that there is risk of non-carcinogenic toxicity. If the factor is smaller than 1, it is considered that the risk is low.

⑥ If MOE with 10% excessive carcinogenic dose is 1/1,000 or higher, it is considered that there is carcinogenic risk. If the value is 1/100,000 or less or excessive carcinogenic probability is 1x10-6 or less, it is considered an ignorable level.

⑦ To calculate risk exerted on the ecosystem by exposure to chemicals, quantitatively and qualitatively predict the degree and frequency of risk to ecosystem by calculating the level of impact on biological species by each medium together with predicted chemical concentration in environment.

⑧ If ecological risk is not expressed with a separate stochastic distribution, display the level of risk with PEC and PNEC ratio, the hazard quotients, If PEC/ PNEC is larger than 1, it is considered that there is a possibility for exposure to the respective substance to cause ecological risk.

Article 9 (Disclosure of Risk Assessment Results) ① According to provisions in Article 15 of the Regulations, results of risk assessment on chemicals can be disclosed through deliberation by Hazardous Chemical Management Committee.

② Assessment report reviewed by Chemical Management Committee shall include the following:

1. Names of chemicals subject to assessment
2. Assessment period
3. Human and ecosystem toxicity assessment
4. Human and ecosystem exposure assessment
5. Assessment on reaction to exposure amount
6. Risk characterization

Article 10 (Time Limit for Re-examination) According to the Regulations on the Issue and Management of Instructions and Standing Operating Procedure (Presidential Instructions No. 248), the time limit for abolition and revision of this Announcement through a review on changes in the law or in actual conditions following the issue of this Announcement shall be by August 31, 2015 <Amended on September 7, 2012>.

Addendum <No. 2012-30, Sep. 7, 2012>

(Enforcement Date) This Announcement shall enter into force as of the day of announcement.

[Attachment 5]

Regulations on Risk Assessment Method and Procedures

Food and Drug Safety Administration Announcement No. 2005- 51 (established on Sep. 28, 2005)
Food and Drug Safety Administration Announcement No. 2007- 87 (established on Dec. 27, 2007)
Food and Drug Safety Administration Announcement No. 2009- 14 (established on May 1, 2009)
Food and Drug Safety Administration Announcement No. 2009- 82 (established on Aug. 24, 2009)
Food and Drug Safety Administration Announcement No. 2009-167 (established on Nov. 9, 2009)
Food and Drug Safety Administration Announcement No. 2012- 28 (established on May 30, 2012)
Food and Drug Safety Administration Announcement No. 2012- 85 (established on Aug. 24, 2012)
Food and Drug Safety Administration Announcement No. 2012-120 (established on Dec. 18, 2012)
Ministry of Food and Drug Safety Announcement No. 2013-36 (established on Apr. 5, 2013)

Chapter 1. General Provisions

Article 1 (Purpose) The purpose of these Regulations is to define details of risk assessment method and procedures in order to ensure scientific, objective and transparent risk assessment on foods, food additives, instruments, containers and packaging (to be referred to as 'foods, etc.' hereinafter) according to Article 15 of Food Sanitation Act and Article 4 of the Enforcement Decree of the same Act and on cosmetics products according to Article 8 of Cosmetics Act and Article 17 of the Enforcement Regulations of the same Act.

Article 2 (Definitions) The terms used in these Regulations shall be defined as follows:

1. The term 'hazard' refers to chemical, microbiological and physical elements remaining in and the state of such elements remaining in foods and cosmetics that have potential risk for human health.
2. The term 'risk assessment' refers to a series of processes to scientifically predict harmful impact and probability of such impact to occur when human body is exposed to hazards existing in foods and cosmetics.
3. The term 'hazard identification' refers to a process to scientifically check potential characteristics of hazards to produce toxicity in human body.
4. The term 'hazard characterization' refers to a process to quantitatively or qualitatively calculate the acceptable amount of human body exposure to hazards based on animal

toxicity data and human toxicity data.

5. The term 'exposure assessment' refers to a process to estimate the level of human exposure based on the data of quantitative and qualitative analysis on hazard to which human body is exposed through food intake or the use of cosmetics.
6. The term 'risk characterization' refers to a process to estimate the degree of risk based on the results of hazard identification, hazard characterization and exposure assessment, and thus to decide the possibility of the current exposure level to cause harmful impact on health. Risk characterization includes uncertainty evaluation.
7. The term 'acceptable amount of human exposure' refers to health-based guidance level at which exposure of human body to the hazard through foods, cosmetics and living environment is considered not to cause harmful impact according to the current scientific standard.

Chapter 2. Risk Assessment on Foods, etc.

Article 3 (Risk Assessment Target and Hazards as Assessment Target) The targets and elements of risk assessment on foods, etc. shall be in accordance with Paragraph 1 and Paragraph 2, Article 4 of the Enforcement Decree of Food Sanitation Act.

Article 4 (Risk Assessment Method) ① Method of risk assessment on foods, etc. is as follows:

1. Identify degree of toxicity and types of impacts caused by exposure to hazards.
2. Decide acceptable amount of human exposure by calibrating uncertainties in animal test results.
3. Quantitatively or qualitatively calculate the amount of level of hazards for exposure through foods.
4. Quantitatively or qualitatively predict the degree and frequency of risk on humans by considering impact on health exerted by hazards and intake of foods containing the hazards, acceptable human exposure amount or level and amount of hazards for exposure through environment other than foods.

② In case the current science and technology level or data are insufficient or prompt risk assessment is required, risk assessment can be carried out as of the following.

1. Comply with or apply decisions and results of hazard identification and hazard characterization carried out by international risk assessment organizations or reliable domestic and foreign risk assessment agencies.
2. In case risk characterization is difficult, risk can be predicted based on hazard

identification and exposure assessment results only.

3. In case such risk as death occurred as a result of food intake, risk can be predicted with hazard identification results only.
4. In case exposure assessment data are insufficient or not available, conduct exposure assessment based on available scientific models.
5. In case the possibility of exposure or risk is considered large for specific groups, conduct risk assessment targeting sensitive and high risk groups, such as children, pregnant women and elders.

③ For detailed risk assessment method according to types and characteristics of hazards, decisions made by Risk Assessment Subcommittee of Food Sanitation Review Committee can be followed.

Article 5 (Risk Assessment Procedures, etc.) ① The Food and Drug Safety Minister shall carry out risk assessment according to the provisions in Article 4 and draw up a report on the results of the assessment.

② When necessary in the course of risk assessment, the Food and Drug Safety Minister can listen to opinions of the related experts.

③ The Food and Drug Safety Minister shall have the results of risk assessment deliberated on by Risk Assessment Subcommittee of Food Sanitation Review Committee. However, in case risk assessment is urgent, deliberation can be carried out afterwards.

④ Notwithstanding Paragraph 3, if deliberation by a respective sub-committee has been completed in standard setting, it shall be regarded that deliberation by Risk Assessment Subcommittee has been completed.

Article 6 (Requesting Risk Assessment to External Organizations, etc.) ① In the event consumers' groups or food-related societies request risk assessment pursuant to Subparagraph 3, Paragraph 1, Article 4 of the Enforcement Decree of Food Sanitation Act, the Food and Drug Safety Minister shall convene Risk Assessment Sub-committee of Food Sanitation Review Committee to deliberate on the possible risks for human health.

② The Food and Drug Safety Minister can request data listed in each of the Subparagraph below to organizations listed in Subparagraph 3, Paragraph 1, Article 4 of the Enforcement Decree of Food Sanitation Act when necessary for deliberation by Risk Assessment Subcommittee of Food Sanitation Review Committee.

1. Objective evidences about risk occurrence or possibility of the risk
2. Types of hazards and the target foods and level of hazard detection
3. Regulatory status of and risk assessment results from foreign countries or international

organizations, such as CODEX

4. Other data necessary in risk assessment

③ In implementing risk assessment, the Food and Drug Safety Minister can request supplementation of necessary data to the organizations listed in Subparagraph 3, Paragraph 1, Article 4 of the Enforcement Decree of Food Sanitation Act.

Chapter 3. Risk Assessment on Cosmetics

Article 7 (Risk Assessment Target and Hazards as Assessment Target) ① The targets of risk assessment on cosmetics are as follows:

1. Cosmetics prohibited or restricted of manufacturing, import, use or display for the purpose of by international organizations or foreign governments upon recognizing the possibility of the products to exert harmfulness on human health
2. Cosmetics from which ingredients or properties recognized by domestic and international research and test organizations to have the possibility to exert harmfulness on human health have been detected
3. Cosmetics produced, manufactured or formulated using new ingredients, properties or technologies or for which safety-related standards have not been established, and thus are considered possible to exert harmfulness on human health

② Hazards to be assessed in risk assessment on cosmetics are as follows:

1. Properties used in cosmetics manufacturing
2. Heavy metals and environmental contaminants and chemical hazards, such as substances generated in the course of manufacturing and storage
3. Physical hazards, such as foreign substances
4. Microbiological hazards, such as germs

Article 8 (Risk Assessment Method) ① The method of risk assessment on cosmetics is as follows:

1. Check the degree of toxicity that can be caused by exposure to hazard and the types of impact.
2. Calibrate uncertainty of animal test and animal alternative test results and decide acceptable human exposure.
3. Quantitatively or qualitatively calculate the amount or level of hazard exposure through cosmetics.
4. Quantitatively or qualitatively estimate the degree and frequency of risk that can be exerted on humans by considering health impact caused by hazards abd the use of

cosmetics containing the hazards, acceptable human exposure amount or level and amount of hazard to which humans are exposed through environment other than the use of cosmetics.

② In the event there are limitations in the currently available science and technology level or data or prompt risk assessment is required, risk assessment on cosmetics can be carried out according to each of the Subparagraph below.

1. Results of hazard identification and hazard characterization carried out by international organizations and reliable domestic and foreign risk assessment agencies can be followed or quoted.
2. In case hazard characterization is difficult, level of risk can be predicted through hazard identification and exposure assessment only.
3. In the event such risk as death has been caused by the use of cosmetics, the level of risk can be predicted through hazard identification only.
4. In case exposure assessment data are not sufficient or not available, exposure assessment can be conducted based on an available scientific model.
5. In case the possibility of exposure is large for specific groups, risk assessment can be conducted targeting sensitive and high-risk groups, such as children and pregnant women.

Article 9 (Risk Assessment Procedures, etc.) ① The Food and Drug Safety Minister shall carry out risk assessment according to provisions in Article 8 and draw up a report on results of the assessment.

② When necessary in the course of risk assessment, the Food and Drug Safety Minister can listen to opinions of the related experts.

③ The Food and Drug Safety Minister shall have the results of risk assessment deliberated on by Cosmetics Subcommittee according to 'Regulations on Politic Advisory Committee of the Ministry of Food and Drug Safety.'

Chapter 4. Internal Delegation of Authority

Article 10 (Internal Delegation of Authority) The Food and Drug Safety Minister delegates authority in relation to each of the following Subparagraph to Director General of National Institute of Food and Drug Safety Evaluation.

1. Risk assessment implementation and report preparation pursuant to Paragraph 1, Article 5 or Paragraph 1, Article 9
2. Listening to experts' opinions pursuant to Paragraph 2, Article 5 or Paragraph 2, Article 9

3. Request for data supplementation pursuant to Paragraph 3, Article 6
4. Other matters recognized to be necessary by the Food and Drug Safety Minister for risk assessment

Article 11 (Establishment and Management of Detailed Guidelines) Director General of National Institute of Food and Drug Safety Evaluation can establish and manage separate detailed guidelines including contents of the following Subparagraph within a range not to be in contradictory to these Regulations.

1. Detailed guidelines for implementation of risk assessment pursuant to Subparagraph 1, Article 10
2. Organization and operation of an advisory committee of experts necessary in the course of risk assessment implementation pursuant to Subparagraph 2, Article 10

Chapter 5. Supplementary Provisions

Article 12 (Supplementary Provisions) Director General of National Institute of Food and Drug Safety Evaluation delegated of authority on implementation of risk assessment in relation to Article 10 shall report the completion of risk assessment report preparation to the Food and Drug Safety Minister.

Article 13 (Time Limit for Re-examination) According to the Regulations on the Issue and Management of Instructions and Standing Operating Procedure (Presidential Instructions No. 248), the time limit for abolition and revision of this Announcement through a review on changes in the law or in actual conditions following the issue of this Announcement shall be by August 24, 2015.

Addenda <No. 2005-51, Sep. 28, 2005>

This Announcement shall enter into force as of the day of announcement.

Addenda <No. 2007-87, Dec. 27, 2007>

This Announcement shall enter into force as of the day of announcement.

Addenda <No. 2009-14, May 1, 2009>

This Announcement shall enter into force as of the day of announcement.

Addenda <No. 2009-82, Aug. 24, 2009>

This Announcement shall enter into force as of the day of announcement.

Addenda <No. 2009-167, Nov. 9, 2009>

This Announcement shall enter into force as of the day of announcement.

Addenda <No. 2012-28, May 30, 2012>

This Announcement shall enter into force as of the day of announcement.

Addenda <No. 2012-85, Aug. 24, 2012>

This Announcement shall enter into force as of the day of announcement.

Addenda <No. 2012-120, Dec. 18, 2012>

This Announcement shall enter into force as of the day of announcement.

Addenda <No. 2013-36, Apr. 5, 2013>

This Announcement shall enter into force as of the day of announcement.

5. Bibliography

Elsa Nielsen, Grete Østergaard and John Christian Larsen, Toxicological risk assessment of chemicals: a practical guide, ISBN 978-084937265-0, Informa Healthcare USA Inc, 2008

Xu-Dong Jia, Ning LI, Zhu-Tian WANG, Yun-Feng ZHAO, Yong-Ning WU and Wei-Xing YAN. 2009. Assessment on dietary melamine exposure from tainted infant formula. Biomed Environ Sci. Apr;22(2): 110~3

Risk Assessment Standard Guidelines, National Toxicity Science Institute Risk Assessment Team, 2007

Human Exposure Assessment Guidelines, National Toxicity Science Institute Human Exposure Assessment Team, 2007

Standards for and Status of Pesticide Residue Limits in Foods, Ministry of Agriculture, Food and Rural Affairs, 2008

Updating the Principles and Methods of Risk Assessment: MRLs for Pesticides and Veterinary Drugs Rome, WHO, 2006

Guidelines for Carcinogen Risk Assessment, Risk Assessment Forum EPA/630/P-03/001FMarch 2005

CODEX Procedural Manual 18th Edition 2008

US EPA, BMDS Downliad page http://www.epa.gov/ncea/bmds/dwnldu.html