[초청강연]

Cancer Risk Assessment of Food Additives and Related Compounds : Current Status in Japan

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1. Introduction

Cancer risk assessment is considered as the process bridging scientific evidence and risk management or linking scientific evidence and achievement of cancer prevention. Risk management involves steps to establish and put into practice strategies for eliminating or minimizing cancer risk from exposure to individual carcinogens.

2. Procedure of cancer risk assessment

In general, the process of risk assessment in chemical safety is categorized into 4 steps, i.e., hazard identification, exposure assessment, dose-response assess and risk characterization. Hazard identification is a process of qualitative evaluation of data concerning the potential of a chemical to produce carcinogenic effects in man. More practically, an attempt to answer the following three questions ; 1) Does the chemical possess carcinogenic potential in experimental animals, 2) What is the mechanism by which the chemical causes cancer in animals and 3) Can the animals data be extrapolated to the human situation Exposure assessment is a process of measuring or estimating real or hypothetical human exposure to particular chemical or an attempt to answer the question, to what extent are humans exposed to the chemical. Dose-response assessment is a process to estimate the mathematical probability that the carcinogenic potential associated with the chemical will be realized under defined conditions of exposure or an

attempt to answer the question, how pronounced could the carcinogenic effect appear in quantitative terms.
Risk characterization, the final step of risk assessment where all relevant information from the first 3 steps is integrated to characterize the carcinogenic risk associated with expected human exposure to the chemical of interest.

3. Animal experiments

Animal data for assessing toxicity including carcinogenicity are obtained from several studies on acute toxicity, short-term toxicity, long-term toxicity/ carcinogenicity, reproductive/ developmental toxicity, genotoxicity, and metabolism/ pharmacokinetics. In a full-scale carcinogenicity study, two species of animas of both sexes are employed.
It is desirable to use animals with normal growth of the same age in weeks, up to the age of 6 weeks. Each group comprises at least 50 males and 50 females. Allocation of the animals to each group is made with the proper random sampling method based on body weight stratification and so on. At least 2 dose groups and a control group are employed for each sex. The administration period last from 24 to 30 months for rats and from 18 to 24 months for mice with administration normally performed 7 days a week.

4. Carcinogenicity studies of food additives and related compounds in Japan

Since 1974, more than 130 food additives and related compounds have been tested for carcinogenicity in Japan. Among them, several compounds such as AF-2, potassium bromate and butylated hydroxyanisole(BHA), proved to be carcinogenic to rodents.
AF-2 was approved for use as a food preservation in Japan in 1965. Subsequently, in 1973 clastogenicity and mutagenicity of this compound was reported and carcinogenicity in mice was demonstrated in 1974. In accordance, AF-2 was prohibited from use as food additive in 1974. This decision was based on the prevailing paradigms at the time regarding carcinogenic risk, namely no existence of threshold for carcinogens, high sensitivity of man to any carcinogen and addition of multi-factorial effects in carcinogenesis. Clastogenicity and mutagenicity

of potassium bromate, a food additive used for baking bread. Induction of kidney tumors in rats after 2-year administration in drinking water at a concentration of 250ppm was then reported in 1982. However, a virtually safe dose(VSD) at the 10-6 risk level was estimated for this compound as 0.95ppm based on a dose-response study in rats.

Furthermore, no evidence of carcinogenicity was observed in rats or mice fed on bread-based diets made from flour treated with 50~75ppm of potassium bromate and analytical chemistry demonstrated that the compound is degradable at the temperature used for baking bread. Based on this and other available evidence, the Ministry of Health and Welfare of Japan therefore permitted the use of potassium bromate at a maximum concentration of 30mg/kg flour for baking, provided that no residue was detectable in the final product. In particular, this decision considered the scientific evidence that the detectable limit of potassium bromate by chemical analysis is far below the VSD value. However, the use of potassium bromate as a food additive for baking bread virtually disappeared through the use of alternative compounds. BHA has been widely used as a food additive to prevent the autooxidation of fats and oils. BHA as well as some other antioxidants are known to inhibit chemical carcinogenesis in rodents when given prior to and/or simultaneously with carcinogen exposure. In 1982, however, it was reported that BHA induced squamous cell carcinomas in the forestomach of male and female rats by feeding at a dose of 2% although its mutagenicity and clastogenicity were largely negative.

5. Genotoxic versus non-genotoxic carcinogens

Experimental and epidemiological evidence indicates that chemicals capable of causing cancer can roughly be divided into two categories, namely, genotoxic and non-genotoxic varieties. It is a general consensus that carcinogenesis involves genetic alterations in somatic cells with activation of oncogenes and/or inactivation of tumor suppresser genes.

Carcinogens are defined as chemicals that can cause either directly or indirectly such genetic alterations in target cells. Concepts of genotoxic/non-genotoxic carcinogens can still contribute to a basic understanding of carcinogenic mechanisms as well as establishment of strategies for cancer risk evaluation from exposure to chemicals. Genotoxic carcinogens are defined as chemicals capable of producing cancer by altering the genetic material of target cells.

Non-genotoxic carcinogens are defined as chemicals capable of producing cancer by some secondary mechanisms not related to direct gene damage in target cells. At present, this classification can not be applied to all instances due to insufficiencies in necessary information or shortage of current knowledge on carcinogenesis. Regarding criteria for genotoxic carcinogen, under bioactivation to reactive electrophilic intermediates it eventually produces DNA-adducts in target cells, it reproducibly gives positive results in a series of in vitro genotoxicity tests, and it induces genetic damage of target cells in short-term in vivo assays. Concerning criteria for non-genotoxic carcinogen, it exhibits no significant genotoxic effects in a series of test systems, it induces specific target lesions characterized by enhanced cell proliferation or sustained cellular hyperfunction or dysfunction in short-term tests, it produces hormonal, metabolic or physiopathological effects underlying the occurrence of target lesions in a series of mechanistic studies, and it enhances target tumor occurrence in animals pretreated with an appropriate initiator. Research projects are required for improvement of cancer risk estimation from exposure to non-genotoxic carcinogens in order to elaborate practical assay systems to confirm that the chemical is not a genotoxic carcinogen, to disclose mechanisms by which chemicals can cause enhanced cell proliferation and sustained cellular hyperfunction or dysfunction in target sites, to elucidate cellular and subcellular mechanisms by which long-standing cell proliferation and cellular hyperfunction or dysfunction can cause gene alterations leading to neoplastic transformation, to clarify subcellular mechanisms and biological significance of active oxygen-mediated carcinogenesis in terms of cancer risk estimation from exposure to chemicals.

6. Acceptable daily intake

The Joint FAO/WHO Expert Committee on Food Additives(JECFA) was established in 1955. The end-points in experimental toxicity studies have been grouped for convenience into effects with functional manifestations only, non-neoplastic morphological characteristics, neoplastic manifestations and reproductive/developmental manifestations. JECFA generally sets the Acceptable Daily Intake(ADI) of a food additive on the basis of the highest no-observed-effect level(NOEL) in animal studies. In calculating the ADI, a safety factor is applied to the NOEL to provide a conservative margin of safety on account of the inherent uncertainties in extrapolating animal toxicity data to

potential effects in the human being and for variation within the human species. When results from two or more animal studies are available, the ADI is based on the most sensitive animal species, i.e., the species that displayed the toxic effect at the lowest dose, unless metabolic or pharmacokinetic data are available establishing that the test in the other species is more appropriate for man.

7. Conclusion

In cancer risk assessment, mechanistic studies involving in vivo genotoxicity are usually required. Recent transgenic animals in which some reporter genes such as lacI and gpt were incorporated may offer a good tool for sensitively detecting in vivo genotoxicity. Two-stage initiation/promotion assay using rodents may be also useful for evaluating the modifying effects of environmental chemicals, especially contributing to the final goal of scientific research on carcinogens and carcinogenesis directed toward achievement of primary cancer prevention.