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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Thirty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives

World Health Organization
Geneva

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization or of the Food and Agriculture Organization of the United Nations

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Joint FAO/WHO Expert Committee on Food Additives

Geneva, 5–14 June 1990

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Monographs containing summaries of relevant data and toxicological evaluations are available from WHO under the title:

Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 28, in press.

Specifications are issued separately by FAO under the title:

Specifications for the identity and purity of certain food additives. (To be published as an FAO Food and Nutrition Paper.)

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

The preparatory work for toxicological evaluations of food additives and contaminants by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is actively supported by certain of the Member States that contribute to the work of the International Programme on Chemical Safety (IPCS).

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. One of the main objectives of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment.

Contents

1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives met in Geneva from 5 to 14 June 1990. The meeting was opened by Dr W. Kreisel, Director, Division of Environmental Health, WHO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Dr Kreisel noted that the recommendations made at previous meetings of the Committee had been used by Member States of FAO and WHO to formulate national regulations on food additives and by the Codex Alimentarius Commission. The Committee's recommendations had probably contributed more to the elaboration of sound national food legislation than had those of any other international body concerned with problems of food technology and safety.

Dr Kreisel drew attention to the forthcoming Joint FAO/WHO Conference on Food Standards, Chemicals in Food, and Food Trade which was scheduled to be held in Rome, in March 1991. This conference would consider certain issues concerning the Codex Alimentarius and the food trade in addition to food additives and contaminants and residues of pesticides and veterinary drugs in food. It would be the first such conference in 20 years and would point the way for future activities of the Committee.

2. General considerations

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955,[1] there have been 36 previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the recommendation made at the thirty-fifth meeting (Annex 1, reference *88*).

The tasks before the Committee were: (a) to undertake toxicological evaluations of certain food additives and contaminants; (b) to review and prepare new or revised specifications for selected food additives; (c) to discuss and advise on matters arising from the eighteenth session of the Codex Alimentarius Commission and the twenty-second session of the Codex Committee on Food Additives and Contaminants (Annex 4); and (d) to discuss the effectiveness and safety of the long-term use of potassium iodate and potassium iodide for fortifying salt, as requested by the Forty-third World Health Assembly (Annex 5).

[1] *Joint FAO/WHO Conference on Food Additives*. FAO Nutrition Meetings Report Series, No. 11, 1956; WHO Technical Report Series, No. 107, 1956.

2.1 Modification of the agenda

Acesulfame potassium was added to the agenda for toxicological evaluation. In addition, the Committee responded to a request made in May 1990 by the Forty-third World Health Assembly, as noted above.

The original list of substances to be evaluated at this meeting included "chymosins A and B from bacterial sources". However, data were received not only on chymosin from a bacterial source (*Escherichia coli* K-12), but also on preparations from a fungus (*Aspergillus niger* var. *awamori*) and from a yeast (*Kluyveromyces lactis*). All three types of chymosin were therefore reviewed by the Committee.

Also included in the original list of substances for evaluation was "α-amylase from *Bacillus subtilis*". Since data were, in addition, received on an α-amylase from *B. stearothermophilus* expressed in *B. subtilis*, both α-amylases were reviewed by the Committee.

The substance "isoascorbic acid" in the original list of substances was evaluated by the Committee under the name "erythorbic acid".

2.2 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives and contaminants, the Committee took into consideration the principles established and contained in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*). This publication, developed in response to repeated recommendations by the Committee, embraces the major observations, comments, and recommendations on the safety assessment of food additives and contaminants contained in the previous reports of the Committee and other associated bodies. The Committee noted that the document reaffirms the validity of recommendations that are still appropriate, and points out the problems associated with those that are no longer valid in the light of modern technical advances.

2.2.1 *The role of pharmacokinetics in the safety evaluation of food additives and contaminants*

The Committee drew attention to the previously published statement on "The use of metabolic and pharmacokinetic studies in safety assessment" in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*), and to the role of such studies in facilitating the extrapolation of data from one species to another, particularly at high levels of exposure.

The safety assessment of a food additive or contaminant is, of necessity, largely based upon the results of studies in experimental animals. Only rarely are adequate human data available to aid this process. The extrapolation of animal toxicity data to humans is complicated by the

occurrence of interspecies differences in both the disposition process (absorption, distribution, metabolism and excretion) and the response mechanisms to chemical substances. This is particularly true of long-term toxicity studies in which high doses are used. In evaluating the safety of chemical substances for use in humans, priority should therefore be given to minimizing such problems, so as to facilitate decision-making. In this regard, the Committee takes account of developments in appropriate areas, such as pharmacokinetics, biochemistry, toxicology and cell and molecular biology, which may be helpful in improving the accuracy of interspecies extrapolation for the purposes of safety assessment.

The Committee stated that it wished to encourage and promote a more widespread use of pharmacokinetic studies in the process of safety evaluation. Attention was drawn to the fact that dosage, as expressed in the conventional manner (e.g., administered dose in mg per kg of body weight), is not necessarily equivalent to systemic exposure and the level producing a toxic effect at the target site. This fact becomes particularly relevant when studies are performed in different animal species and data are extrapolated to humans, because of species, gender, and strain differences in the absorption, tissue distribution, biotransformation and excretion processes. Furthermore, the use of very high dose levels (e.g., the maximum tolerated dose) in long-term toxicity studies may cause phenomena such as "metabolic switching" due to the saturation or exhaustion of the normal metabolic pathways or the induction of enzymes, which can alter the "normal" biotransformation processes. The extent of such metabolic deviations may vary from species to species, and can have a large effect on exposure to the compound of interest at the target site.

The Committee recommended that appropriate pharmacokinetic data from various species, including where possible humans, should accompany future submissions of data from short-term and long-term studies. The Committee pointed out the advantages of including the investigation of pharmacokinetic parameters in acute studies before commencing short-term and long-term studies, as the results obtained can be of value in study design. Additional animals might be required in short-term and long-term studies, to be used primarily for investigating toxicokinetic and metabolic parameters. Such studies should be designed in order to determine the levels of systemic exposure at different dose levels used and whether metabolic switching and enzyme induction occur. The availability of such data will facilitate interspecies assessment of systemic exposure to a given compound, which will result in the generation of a much more reliable "safety factor" than one based upon dosage considerations alone.

2.2.2 *Carcinogenic food contaminants*

The Committee was asked to review the effects of benzo[*a*]pyrene, a ubiquitous carcinogenic chemical. A major reason for the occurrence of benzo[*a*]pyrene in food is the use of certain types of heat processing, such

as smoking, baking and cooking. Heat processing can result in the production of numerous other carcinogenic polycyclic aromatic hydrocarbons, various nitrosamines, aminoimidazoazarenes (in cooked meats), and various heterocyclic amines formed as pyrolysis products of certain amino acids. Toxicologists are therefore faced with the evaluation of the potential hazard of a large range of chemicals that occur as contaminants in human food and are carcinogenic in animals. The Committee emphasized, however, that toxicological effects other than carcinogenicity are not necessarily less important in the safety evaluation of such compounds.

Benzo[*a*]pyrene invariably occurs in association with many other carcinogenic polycyclic aromatic hydrocarbons. Attention has been focused on benzo[*a*]pyrene mainly because it has been analysed more frequently and subjected to extensive toxicological investigation. Recently interest has been focused on other compounds produced during cooking of meat, in particular certain heterocyclic amines and aminoimidazoazarenes.

Advances in analytical chemistry and ongoing programmes of testing are disclosing an increasing number of carcinogenic contaminants in foods. Potentially carcinogenic nitrosamines may be produced in foods treated with nitrites (e.g., bacon) or exposed to nitrogen oxides (e.g., barley, during roasting for beer production). Other examples are the carcinogenic contaminants aflatoxins and ochratoxin A.

Various suggestions have been made over several decades that certain gastrointestinal tumours in humans are associated with the consumption of smoked foods. All the epidemiological observations have, however, been considered equivocal by the scientific community. Some reassurance that the risks are low is provided by the observation that contaminants in smoked foods are usually present at very low levels, and are associated with food processes dating back many centuries.

The Committee considered that potentially carcinogenic compounds in food should be identified and data collected on their occurrence, the influence of food technology processes on their levels in food, and their carcinogenic properties, so as to set priorities for assessing their safety.

2.2.3 *Safety assessment of flavouring agents*

The Committee reviewed the safety assessment of flavouring agents with respect to the particular features of this group of food additives, namely, the number of substances concerned, their diversity, and the low levels of use of many flavouring agents. Factors that should be considered in the safety evaluation of these compounds include: data from toxicological studies in animals and short-term tests for mutagenicity and clastogenicity, results from studies on metabolism and structure–activity relationships, the level of usage, the consumption ratio (Annex 1, reference *83*, Annex 4),

the source of the flavouring agent and data on the extent and frequency of human exposure (Annex 1, reference *76*).

In assessing the safety of flavouring agents, the Committee also takes into account the findings of other groups and institutions involved in the evaluation of these agents.

At its present meeting, the Committee considered the safety of three allyl esters of fatty acids, which were placed on the agenda on the basis of application of the method used in setting priorities for the safety review of food flavouring ingredients (Annex 1, reference *83*, Annex 4). The Committee concluded that a group Acceptable Daily Intake (ADI) should be allocated to the three esters on the basis of the allyl alcohol moiety, because they are rapidly hydrolysed and the observed toxic effects are due to this moiety. At the same time, it was recognized that a large number of other allyl esters of fatty acids are rapidly hydrolysed in a similar manner, so the same considerations should apply to them. It would have been helpful if data on these other substances had also been collected, so that they could have been considered for inclusion in the group ADI.

The Committee concluded that the safety evaluation of a specific flavouring agent would be facilitated by consideration of the structurally related group as a whole. Therefore, in most cases, all members of a structurally related group should be placed on the agenda, even if some of them are not in the highest priority level for evaluation.

2.3 Principles governing the establishment and revision of specifications

2.3.1 *Revision of the "Guide to specifications"*

The "General methods" section of the *Guide to specifications* (Annex 1, reference *65*) has not been updated since 1983. The need to update the general methods, to take account of changes in specifications, methodologies, and analytical techniques adopted since the last revision, was stressed at the Committee's last three meetings at which food additives were evaluated (Annex 1, references *77, 83* and *88*).

At its present meeting, the Committee considered a draft for a revised *Guide to specifications* to be published by FAO. The proposed changes included incorporation into the revised "General methods" section of the general methods for the analysis of food colours, which were prepared at the Committee's twenty-eighth meeting and partially revised at the thirty-first meeting (Annex 1, references *66* and *77*), and of other methods whose development had been requested at past meetings, such as those for infrared spectroscopy, gas chromatography (using headspace sampling) and microbiological tests. The Committee agreed to the proposed changes and took them into account in preparing specifications at its present meeting.

The Committee noted that the "General notices" section of the *Guide to specifications* – which provides guidance and definitions to assist in the preparation of specification monographs – was also being revised to take into account the changes and current developments in specifications, and a separate guide for enzyme preparations was being prepared.

2.3.2 *Microbiological criteria*

In revising the specifications of xanthan gum and establishing specifications for gellan gum, both of which are derived from microbiological sources, the Committee considered the microbiological criteria that should be specified. The Committee concluded that it was sufficient to specify limits and tests for total plate count, yeasts and moulds, coliforms, and salmonellae for these gums. These microbiological criteria are used widely for natural substances and are considered sufficient for the purpose of quality assurance. Additional requirements for the specific identity of the microorganisms in the final product were not considered necessary where the manufacturing process would essentially preclude such contamination.

2.4 Principles governing consideration of enzyme preparations from genetically modified microorganisms

The Committee has, on several previous occasions, addressed problems associated with the formulation of specifications for enzyme preparations used in food processing and manufacture. At its present meeting, the Committee had, for the first time, been asked to evaluate specific enzyme preparations from genetically manipulated source organisms. Consideration of the method of production and the specification of identity and purity is an important part of the safety evaluation of any food additive. The use of genetic modification techniques introduces factors additional to those associated with conventionally produced enzyme preparations.

Some assurance as to safety may be derived from the similarity of the active component of an enzyme preparation from transgenic sources to that from enzyme preparations produced conventionally and previously evaluated and considered to be safe. It is also important to ensure that harmful impurities have not been introduced into the final product by the organism serving as the source of the genetic material, during the process used in cloning the genetic material to be transferred or the construction of the production organism, or otherwise as a result of the genetic manipulation techniques employed. The final product should be characterized accordingly, and attention paid, for example, to the possible presence of viable cells of the source (transgenic) organism, the expression plasmid or vector, DNA fragments and non-enzyme protein.

The possibility of a latent capacity for toxin production by the donor or the host organism must also be taken into account. In this regard, the identity of the organisms serving as donors and intermediate and final hosts of the

transposed genetic material is crucial. A previous history of human exposure to, or investigation of, these organisms will be important in determining the extent of testing required, including toxicological testing of the end-product. Whenever such a product is to be evaluated by the Committee, a fully documented taxonomic history of the organisms concerned, together with detailed methods for their identification, should be provided. Furthermore, the use of national and international culture collections as sources of reference material by manufacturers to assist in the identification of microorganisms used commercially should be encouraged.

The Committee prepared an addendum to its previously published "General specifications for enzyme preparations used in food processing" (Annex 1, reference *69*) to reflect the additional concerns relating to enzyme preparations from genetically manipulated organisms. The Committee noted that the possibilities afforded by the techniques of biotechnology and genetic manipulation had implications not only for the development of new sources of enzymes but also for the production of other classes of food additives.

3. Comments on specific food additives and contaminants

The Committee evaluated a number of food additives and contaminants for the first time and re-evaluated several substances considered at previous meetings. Information on the evaluations and on specifications is summarized in Annex 2. Details of further toxicological studies and of other information required or desired for certain substances are given in Annex 3.

3.1 Specific food additives

3.1.1 *Antioxidants*

Butylated hydroxytoluene (BHT)

Butylated hydroxytoluene (BHT) was last evaluated at the thirtieth meeting of the Committee (Annex 1, reference *73*) when a temporary ADI of 0–0.125 mg per kg of body weight was established. At that time, the Committee based its evaluation of BHT on a one-generation reproduction study in rats, in which a no-effect level of 25 mg per kg of body weight per day was observed. As a long-term study in Wistar rats involving exposure to BHT *in utero* had shown hepatocarcinogenicity in male rats at a high dose level, in contrast to several previously reviewed single-generation long-term studies in Fischer 344 and Wistar rats, the Committee requested further investigation of the hepatocarcinogenicity of BHT in rats after *in utero* exposure. The Committee also noted that, in several studies from one laboratory, feeding of high doses of BHT caused haemorrhage in rats given

a diet containing low amounts of vitamin K, which suggested an anti-vitamin K effect of BHT. The Committee therefore requested further studies on the mechanism of the haemorrhagic effect of BHT.

The requirements of the Committee have been partially met. In further studies on the haemorrhagic effect of BHT in male Sprague-Dawley rats, the compound caused a very rapid decrease in levels of vitamin K-dependent coagulation factors in the plasma, while platelet aggregation did not seem to be affected initially. The causative agent is probably a metabolite of BHT, as it was demonstrated that inhibitors of hepatic drug metabolism reduced the effect on coagulation factors. The Committee noted that high doses of BHT are required to cause haemorrhage in vitamin K-deficient rats; it did not consider this effect to be critical with respect to the safety evaluation of BHT as a food additive in the human population.

The Committee was informed that a study had been initiated on the development and role of hepatic changes in long-term toxicity in male Wistar rats after exposure to BHT *in utero*. The Committee reviewed results from a "range-finding" study and from the main study in which the F_1 generation had been exposed to BHT in the diet for 7 months after weaning. The study design was very similar to that of the previously reported long-term study in which rats were exposed to the compound *in utero*.

Additional studies have confirmed that BHT is not genotoxic, and several short-term toxicity studies in rats have indicated that doses of up to 25 mg per kg of body weight per day have no toxic effects on the liver; high doses (250 mg per kg of body weight per day and above) are required to induce hepatic necrosis. In addition, the Committee noted that, in contrast to phenobarbital and DDT, BHT administered for 22 weeks did not increase the incidence of hepatocellular carcinomas in Wistar rats after initiation with dimethylnitrosamine.

The Committee extended the previously established temporary ADI of 0–0.125 mg per kg of body weight pending the results of the ongoing long-term study in rats involving *in utero* exposure to BHT. The Committee requested the final results of this study for re-evaluation of BHT in 1994.

An addendum to the toxicological monograph was prepared. The existing specifications for BHT were revised.

tert-Butylhydroquinone (TBHQ)

tert-Butylhydroquinone (TBHQ) was previously evaluated at the nineteenth, twenty-first, and thirtieth meetings of the Committee (Annex 1, references *38*, *44*, and *73*). At the thirtieth meeting, a temporary ADI of 0–0.2 mg per kg of body weight was established based on the results of a long-term feeding study in dogs in which a no-effect level of 1.5 g/kg of the diet was observed. The Committee requested additional information for re-evaluation of the compound in 1990, including the results of lifetime