World Health Organization
Organisation mondiale de la Santé

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Reports of advisory bodies and related issues

Report on meetings of expert committees and study groups

Report by the Director-General

The Director-General submits this report on two meetings of expert committees[1] and one meeting of a study group.[2] It summarizes the recommendations of each expert committee or study group meeting, with emphasis on their potential contribution to improving the public health situation in Member States, and implications for WHO's programmes.

The Executive Board is invited to comment on the Director-General's report.

[1] In compliance with paragraph 4.23 of the Regulations for Expert Advisory Panels and Committees (*WHO Basic Documents*, 41st ed., 1996, p. 104).

[2] In conformity with resolution EB17.R13, paragraph 4.

CONTENTS

EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Joint FAO/WHO Expert Committee on Food Additives
Rome, 4-13 June 1996[1]

Summary of conclusions and recommendations

1. The Committee made recommendations on residues of several veterinary drugs in food. The Committee also discussed procedures for assessing the effects of antimicrobial drug residues in food on the human intestinal microflora, including *in vitro* methods, such as determination of minimum inhibitory concentrations and continuous and semi-continuous culture systems, and *in vivo* methods, such as studies on conventional laboratory animals, human microflora associated with germ-free rodents, and volunteers. These methods differ in their relevance and practicality, and the Committee encouraged the development of better *in vitro* and *in vivo* methods that are relevant for determining the effects of low concentrations of antimicrobial agents on the human gastrointestinal microflora.

2. The Committee evaluated two adrenoceptor agonists (clenbuterol and xylazine), two anthelminthic agents (abamectin and moxidectin), seven antimicrobial agents (chlortetracycline, oxytetracycline, tetracycline, neomycin, spiramycin, thiamphenicol and tilmicosin), and two insecticides (cypermethrin and α-cypermethrin). Acceptable Daily Intakes (ADIs) or temporary ADIs were established for all of these substances except xylazine. The Committee recommended Maximum Residue Limits (MRLs) in appropriate tissues (muscle, liver, kidney and fat), milk and/or eggs for all substances except xylazine.

3. Summaries of the toxicological and related information that was reviewed and which served as the basis for assessing the safety of the veterinary drugs considered have been published separately by WHO.[2] Summaries of the residue information that was reviewed and served as the basis for the recommended MRLs have been published by FAO.[3]

Significance for public health policies

4. The Committee emphasized the public health significance of the risk assessment of chemicals used in food, including the complexity of the process, which requires assembling and analysing all the relevant data; interpreting studies of carcinogenicity, mutagenicity, reproductive toxicity, teratogenicity, antimicrobial activity and other effects; extrapolating to humans effects observed in experimental animals; and assessing risks to humans based on available toxicological, epidemiological and microbiological data.

5. Although all Member States face the problem of assessing these risks, only a few scientific institutions can undertake such assessments at this stage; hence the importance of providing all Member States with valid information both on the general aspects of risk assessment and on the specific veterinary drugs that are covered in this report.

6. The recommendations of the Committee are used by the Codex Alimentarius Commission for setting international standards, including limits on residues of veterinary drugs in foods. Such standards are established only for substances that have been evaluated by the Committee and have been allocated an ADI. This ensures that food commodities in international commerce meet strict safety standards.

[1] WHO Technical Report Series, No. 876 (in press).

[2] *Toxicological evaluation of certain veterinary drug residues in food*. WHO Food Additives Series, No. 38, 1996.

[3] *Residues of some veterinary drugs in animals and foods*. FAO Food and Nutrition Paper 41/9, 1997.

Implications for the Organization's programmes

7. The evaluation of chemicals in food by the Committee is an ongoing activity. Four meetings of the Joint FAO/WHO Expert Committee on Food Additives are scheduled in the current biennium, two on residues of veterinary drugs in food and two on food additives and contaminants.

8. WHO cooperates in and contributes to the Joint FAO/WHO Food Standards Programme, which administers the Codex Alimentarius Commission. Because evaluations by the Committee are required before proposed standards can move forward, its evaluations are critical to the success of the work of the Codex Alimentarius Commission.

9. Regional offices and WHO Representatives in countries make use of the evaluations performed by the Committee when advising Member States on food safety regulatory programmes.

WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Forty-seventh report
Geneva, 7-11 October 1996[1]

Summary of conclusions and recommendations

10. The WHO Expert Committee on Biological Standardization reviews developments in the field of biological substances used in medicines, establishes international reference materials and develops requirements and guidelines for the production and control of such biologicals.

11. The use of international reference materials for designating the activity or identity of biological preparations used in prophylaxis, therapy or diagnostics, ensures comparability of the activity of these substances worldwide, and the reliability of diagnostic procedures. Based on the results of international collaborative studies, the Expert Committee established 20 new or replacement international reference materials, and eight were discontinued.

12. In addition, the Committee adopted three new documents, revised requirements for cell substrates used for the production of biologicals, guidelines for the production and control of the acellular pertussis vaccines, and guidelines for assuring the quality of DNA vaccines. All three were adopted after extensive worldwide consultation.

13. The revised requirements for use of animal cells for the production of biologicals take into account the latest available data. Considerable emphasis is placed on testing for extraneous agents. There is also a reassessment of the risk posed by contaminating DNA deriving from continuous cell lines used in the production of biologicals. Based on the current state of knowledge, the Committee recommended that this DNA should now be considered more as a contaminant than as a significant risk factor requiring its removal to extremely low levels, and amended the requirements accordingly.

14. In view of the lack of consensus about the antigenic composition of an ideal pertussis vaccine and the fact that no unequivocal immunological correlates of protection against pertussis had been demonstrated, nor a generally accepted animal model validated to predict the clinical efficacy of these vaccines, the Committee emphasized the need for continued research in this area. However, because of the need for guidance, the Expert Committee adopted guidelines on the production and control of acellular pertussis vaccines which allow for further developments.

[1] WHO Technical Report Series, No. 878 (in press)

15. The Expert Committee also recognized the importance of providing guidance to national control authorities on the rapidly developing field of DNA vaccines. Although this radically new approach to vaccination offers a number of advantages, there are also several potential safety issues which need to be addressed. The guidelines indicate appropriate methods for control of the manufacture and testing of DNA vaccines and the type of information expected in support of applications for clinical trials and licensing.

Significance for public health policies

16. WHO's biological standardization activities are important to both developing and developed countries. The greatly increased complexity and expansion of the biologicals field, and its sensitivity and high profile internationally with regard to safety issues, call for establishment of effective control measures based on a firm scientific foundation. The Expert Committee noted that a review of the scientific basis of standardization and quality control of biologicals had been conducted on behalf of the National Biological Standards Board of the United Kingdom, the report of which had been presented to WHO. The review had been undertaken with the collaboration of WHO and because its conclusions have important implications internationally, the Expert Committee endorsed a proposal to issue the report under the auspices of WHO to permit its wide dissemination globally.[1]

17. The concept of using well-characterized preparations of biological substances as references against which batches of research materials and manufacturers products are assessed remains fundamental to assuring the quality of biological medicines and diagnostics, whether prepared by conventional or novel biotechnologies. International reference materials established by WHO are primary standards against which national or regional standards are calibrated. Their wide use emphasizes the key role of these materials in harmonizing the quality of biologicals internationally and, together with the implementation of recommendations for the production and quality control of biologicals, provide the foundation for the deployment of biologicals in public health programmes.

Implications for the Organization's programmes

18. The Expert Committee on Biological Standardization provides up-to-date recommendations on biological substances used in medicine, and ensures the availability of necessary international reference materials. Its work enables the Organization to fulfill its constitutional responsibilities in this area.

19. The importance to national control authorities and manufacturers of the recommendations and information in the Committee's Report, including those on international reference materials, stresses the need for the Report to be made available as quickly as possible, and also widely distributed.

20. The observations, conclusions and recommendations of the Expert Committee also have important implications for a number of WHO programmes, in particular:

- the Global Programme for Vaccines and Immunization with respect to the provision of up-to-date requirements and reference preparations for assuring the safety and efficacy of vaccines;
- the Programme on Health Technology, especially with respect to the provision of reference preparations for standardizing assays used for assuring the virological safety of blood and blood products;
- the Special Programme on Research and Training in Tropical Diseases with respect to the preparation of guidance on the characterization and quality of candidate vaccines against malaria.

[1] Biological standardization and control. Document WHO/BLG/97.1.

HIGH DOSE IRRADIATION

Joint FAO/IAEA/WHO Study Group (Wholesomeness of food irradiated with doses above 10 kGy) Geneva, 15-19 September 1997

Summary of conclusions and recommendations

21. Food irradiated to any dose appropriate to achieve the intended technological objective is both safe to consume and nutritionally adequate. This conclusion is based on extensive scientific evidence that this preservation process can be used effectively to eliminate spores of proteolytic strains of *Clostridium botulinum* and all spoilage microorganisms, that it does not compromise the nutritional value of the foods, and that it does not result in any toxicological hazard. Recognizing that in practice the doses applied to eliminate the biological hazards would be below those doses that might compromise sensory quality, the Study Group concluded that no upper dose limit need be imposed. Accordingly, irradiated foods are deemed wholesome throughout the technologically useful dose range from below 10 kGy to envisioned doses above 10 kGy.

22. The substantial benefit to food safety and food availability that would accrue directly from the broad application of food irradiation requires that steps should be taken to put this technology into wider practice. These steps will involve standardization, communication, and education. To this end, WHO, in collaboration with FAO and IAEA, should organize and participate in appropriate training courses and workshops that educate food regulators and food workers about the role food irradiation could, and should, play as a control measure in the frame of the application of the hazard analysis and critical control point system.

23. WHO should also take the lead in advising international agencies and national ministries of health on implementing integrated strategies, including food irradiation, for preventing the transnational spread of pathogens in food and animal feed, for controlling foodborne illnesses, and for enhancing the availability of safe and nutritious foods.

24. For details regarding the conclusions and recommendations of the Study Group, please refer to the Annex.

Significance for public health policies

25. With the reconfirmation of the safety and nutritional adequacy of food treated with doses up to 10 kGy, and the confirmation that high dose irradiation (doses >10 kGy) does not compromise the safety and nutritional adequacy of food so treated, food regulatory agencies should give consideration to the application of food irradiation technology not only for public health benefits but also, in appropriate cases, to reduce post-harvest food losses and as a quarantine treatment.

26. Food irradiation is not seen by WHO as a panacea for the numerous problems related to the food supply, but it has, under certain circumstances, a role to play in promoting food safety, preventing the transnational spread of pathogens in food and animal feed, and reducing food losses, thus contributing to food security. Food irradiation could be seen as one of the most important contributions of food science and technology to public health, comparable only to milk pasteurization. Since the availability and safety of food are important components of the primary health care approach, the Study Group expressed its concern that the unwarranted rejection of this process, often based on a lack of understanding of what food irradiation entails, might hamper its use in those countries which may benefit most.

27. Recognizing the potential public health benefits of food irradiation at an early time, WHO has been collaborating with FAO, IAEA and the scientific community, since 1961 to establish whether foods so treated are safe and nutritious. Since then, nine international expert meetings and one major international conference have been held. The Study Group meeting in 1997 was the last step in this 36-year process. Despite WHO's

efforts, governments and the food industry have been slow in applying this technology, of considerable health and economic benefit. So far, only some 40 countries have regulations regarding the irradiation of food.

Implications for the Organization's programmes

28. Through WHO's leadership during 36 years of international collaboration, the safety and nutritional adequacy of irradiated food has now been firmly established. WHO will continue to monitor scientific development in this field and review, if necessary, any serious report suggesting that irradiation-induced hazards have been identified. Its main commitment will, however, be in the area of advocacy, encouraging Member States, the food industry and consumers to take advantage of the health and economic benefits offered by the responsible application of this technology.

ANNEX

Joint FAO/IAEA/WHO Study Group[1]

HIGH DOSE IRRADIATION

Geneva, 15-19 September 1997

CONCLUSIONS

Wholesomeness: safety and nutritional adequacy

The Study Group concluded that food irradiated to any dose appropriate to achieve the intended technological objective is both safe to consume and nutritionally adequate. This conclusion is based on extensive scientific evidence that this preservation process can be used effectively to eliminate spores of proteolytic strains of *Clostridium botulinum* and all spoilage microorganisms, that it does not compromise the nutritional value of the foods, and that it does not result in any toxicological hazard. Recognizing that in practice the doses applied to eliminate the biological hazards would be below those doses that might compromise sensory quality, the Study Group concluded that no upper dose limit need be imposed. Accordingly, irradiated foods are deemed wholesome throughout the technologically useful dose range from below 10 kGy to envisioned doses above 10 kGy.

Substantial equivalence

The Study Group in assessing risk concluded that irradiation to high doses is essentially analogous to conventional thermal processing, such as the canning of low acid foods, in that it eliminates biological hazards (i.e. pathogenic and spoilage microorganisms) from food materials intended for human consumption, but does not result in the formation of physical or chemical entities that could constitute a hazard. Abundant and convincing data indicate that high-dose irradiated foods do not contain either measurable levels of induced radioactivity or significant levels of any radiolysis products distinct from those found in unirradiated foods. The theoretical maximum levels that might be formed would be so low as to be of no toxicological consequence. None of the toxicological data derived from extensive animal feeding studies reveal any teratogenic, carcinogenic, mutagenic, or other harmful effects that are ascribable to high-dose irradiated foods. For these reasons, the application of "risk assessment" in the currently accepted sense[2] is not appropriate to the toxicological assessment of foods preserved by high-dose irradiation. In this context, the concept of "substantial equivalence" may be more appropriate. High-dose irradiated foods are indeed as safe as food materials sterilized by thermal processing, which humans have been eating for over a century.

Applications

The Study Group concluded that high-dose irradiation, following both good manufacturing practices and good irradiation practices, could be applied to several types of foods to improve their hygienic quality, to make them shelf stable, and to produce special products. It is envisaged that these foods could include, but not be limited to: spices and other dry food ingredients; prepackaged precooked foods that could be stored at ambient temperature for extended periods; and sterilized meals for specific target groups (such as disaster victims, campers, and the immunocompromised). Components of all classes of foods whose sensory qualities are not

[1] The full report of the Study Group is in preparation for publication in the WHO Technical Report Series.

[2] The Codex Alimentarius Commission adopted in 1997, on an interim basis, the following definition for risk assessment: "A scientifically based process consisting of the following steps: (i) hazard identification; (ii) hazard characterization; (iii) exposure assessment; (iv) risk characterization".

compromised could be irradiated to high doses, either singly or in any combination. Packaging materials that are technically applicable and approved would be used as appropriate.

Global standardization

The Study Group concluded that appropriate steps need to be taken to establish the technological guidelines implied by these conclusions, and to communicate them through Codex Alimentarius standards.

RECOMMENDATIONS[1]

The substantial benefit to food safety and food availability that would accrue directly from the broad application of food irradiation requires that steps should be taken to put this technology into wider practice. These steps will involve standardization, communication, and education.

WHO, in collaboration with FAO and IAEA, should:

- coordinate the preparation of documentation and the drafting of appropriate technical language for adoption of standards by the Codex Alimentarius Commission;

- prepare appropriate brochures and documents that integrate food irradiation into existing guidelines and rules governing the safe production, distribution, and handling of food in order to minimize the spread of biological contamination and incidence of foodborne illnesses;

- organize and participate in appropriate training courses and workshops that educate food regulators and food workers about the role food irradiation could, and should, play as a control measure in the framework of the application of the hazard analysis and critical control point system.

WHO should take the lead in advising international agencies and national ministries of health on implementing integrated strategies, including food irradiation, for preventing the transnational spread of pathogens in food and animal feed, for controlling foodborne illnesses, and for enhancing the availability of safe and nutritious foods.

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[1] These recommendations reflect the collective views of the Study Group and do not necessarily represent the decisions or the stated policy of WHO.