

# Expert committees and study groups<sup>1</sup>

## Report by the Secretariat

### EVALUATION OF CERTAIN FOOD ADDITIVES

#### Sixty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives<sup>2</sup> Rome, 20–29 June 2006

#### Main recommendations

1. The Committee made recommendations on the safety of several food additives and contaminants and prepared or reviewed specifications for a number of them. It also made several general recommendations, in particular on the principles of safety assessment of flavouring agents and enzymes produced by genetically modified organisms.
2. The Committee evaluated several food additives, some of them for specifications only, and established acceptable daily intakes for four. It also evaluated the health risk of four food contaminants and established tolerable intakes where appropriate.
3. Summaries of the toxicological and related information upon which the safety assessments of the compounds were made will be published by WHO.<sup>3</sup> Summaries of the identity and purity of food additives and flavouring agents will be published by FAO.<sup>4</sup>

#### Significance for public health policies

4. Although all Member States face the problem of assessing potential risks of chemicals in food, only a few national or regional scientific institutions can assess the relevant toxicological and related data. It is therefore important to provide Member States with valid information on the general aspects of risk assessment and on specific evaluations of food additives and flavourings covered in this report.

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<sup>1</sup> The Regulations for Expert Advisory Panels and Committees provide that the Director-General shall submit to the Executive Board a report of expert committees containing observations on the implications of the expert committee reports and recommendations on the follow-up action to be taken.

<sup>2</sup> WHO Technical Report Series, No. 940, in press.

<sup>3</sup> Safety evaluation of certain food additives. WHO Food Additives Series.

<sup>4</sup> Compendium of food additive specifications, FAO Food and Nutrition Paper.

The Committee's complex work in reaching an international consensus on the evaluation of these compounds means that no other body has such comparable influence on public health decisions related to food safety.

5. The Committee's work identifies and, if possible, quantifies the public health significance of food additives, flavouring agents and contaminants in food through a scientific risk assessment agreed by consensus among international experts. It highlights the complexity of the process, which includes: assembling and analysing all relevant data; interpreting studies of, for example, general toxicity, carcinogenicity, genotoxicity, reproductive toxicity, and teratogenicity; extrapolating to humans the effects observed in experimental animals; and characterizing hazards to humans based on available toxicological and epidemiological data.

6. The Committee's recommendations are used by the Codex Alimentarius Commission for setting international food safety standards. Such standards are established only for substances that have been evaluated by the Committee and allocated an acceptable daily intake, tolerable intake or other relevant safety statement. This ensures that food commodities in international trade meet strict safety standards. The advice provided by the Committee is also used by Member States in setting national/regional food safety standards.

### **Implications for the Organization's programmes**

7. The Committee's evaluation of chemicals in food is a continuing activity. Three meetings of the Joint FAO/WHO Expert Committee on Food Additives (two on food additives and contaminants, and one on residues of veterinary drugs in food) have been scheduled for the biennium 2006–2007.

8. WHO is a partner in the Joint FAO/WHO Food Standards Programme, whose principal organ is the Codex Alimentarius Commission. The Committee's work is crucial to that of the Commission.

9. Regional offices and WHO Representatives also make use of the Committee's evaluations when advising Member States on food safety regulatory programmes.

## **TOBACCO PRODUCT REGULATION**

### **Report of the third meeting of the WHO Study Group on Tobacco Product Regulation<sup>1</sup> Kobe, Japan, 28–30 June 2006**

10. Regulation of tobacco products is in its infancy in many parts of the world. However, the WHO Framework Convention on Tobacco Control has set the stage and laid the groundwork for future regulation of the contents, emissions, disclosure, packaging and labelling of tobacco products.

11. This report summarizes the outputs of the third meeting of the WHO Study Group on Tobacco Product Regulation, which focused on: contents and design features of tobacco products: their relationship to addictiveness and consumer appeal; candy-flavoured tobacco products: research needs and recommended actions by regulators; biomarkers of tobacco exposure and of tobacco smoke-

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<sup>1</sup> WHO Technical report series, No. 945.

induced health effects; setting maximum limits for *N*-nitrosornicotine and 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone in cigarette smoke

## **Contents and design features of tobacco products: their relationship to addictiveness and consumer appeal**

### **Main recommendations**

12. The harm caused by tobacco products is a function of their toxic emissions and the extent and patterns of use. Patterns of use, in turn, are related to addictiveness and consumer appeal. Tobacco industry documents and expert evaluation reveal extensive manipulation of contents and designs to increase addictiveness and appeal. For example, the addictive impact of nicotine can be increased by contents and designs that increase the free-base fraction of nicotine, and flavourings such as cherry and cloves can be used to appeal to target populations.

13. The Study Group recommended that tobacco product contents and designs should be evaluated from the perspective of addictiveness and consumer appeal to provide the foundation for potential restrictions on these aspects.

### **Significance for public health policies**

14. The significance for public health policies includes maintaining, increasing and implementing standards for tobacco product contents, designs and emissions related to addictiveness and consumer appeal, thereby supporting efforts to reduce prevalence of use and possibly toxicant intake among users. Combined with other tobacco-control elements and actions, such policies should lead to a reduction in tobacco use and associated disease.

### **Implications for the Organization's programmes**

15. Given the variety of ingredients and design features of tobacco products, WHO's surveillance and research efforts will need to focus on the effects of tobacco initiation and cessation on health. Research will need to be conducted on the contents and design features that may contribute to addictiveness and consumer appeal, and, hence, to more prevalent, persistent and deadly use. A timetable for goal achievement will also be needed, taking into account resources and capacity, and the need for revision and new targets as objectives are attained.

## **Candy-flavoured tobacco products: research needs and recommended actions by regulators**

### **Main recommendations**

16. The use and marketing of candy-flavoured additives in tobacco products should be restricted. The Study Group's report identifies current packaging styles and flavour varieties and provides guidelines and recommendations for health professionals working for the cessation of tobacco use, and for tobacco-product manufacturers.

17. Tobacco manufacturers should be required to disclose additives, including candy-flavoured additives in tobacco products by brand and level. Health-risk reduction claims should be prohibited. The use of candy-flavoured additives in new tobacco brands should be prohibited. For tobacco companies or brands currently using flavoured additives, limits should be set on any additive that

contributes to addiction, initiation or increase in second-hand smoke exposure, or discourages cessation. These recommendations and other strategies to regulate candy-flavoured tobacco products should be part of an overall strategy to regulate the contents, emissions, and design of tobacco products and to reduce the disease burden.

### **Significance for public health policies**

18. Analyses of the tobacco industry's internal documents indicate the widespread use of additives to change the perception and impact of tobacco smoke delivery and environmental tobacco smoke. It is in the interests of public health to stipulate that candy-flavoured additives should not be used to make addictive drugs more appealing or to mask the harmful effects of product use and exposure. Although tobacco companies deny targeting youth, published research suggests that candy-flavoured additives are a significant factor in attracting young and inexperienced smokers.

19. Published research has also revealed the use of new flavour-delivery mechanisms such as plastic pellets embedded in cigarette filters. Failure to disclose the use of flavour-delivery technologies raises additional health concerns and emphasizes the frequently unrecognized role of flavour and additive delivery in product design. These findings support the need for appropriate government regulations to identify and evaluate the potential harm both to the individual and to populations.

### **Implication for the Organization's programmes**

20. A WHO policy recommendation encouraging the regulation of candy-flavoured additives would be an essential component of a comprehensive plan to regulate tobacco products. WHO should stimulate and promote research to evaluate the effects and toxicity of new delivery mechanisms such as the flavoured embedded pellet. More population-based research is needed on the effect of candy flavourings and other additives on initiation, addiction, use and exposure.

### **Biomarkers of tobacco exposure and of tobacco smoke-induced health effects**

#### **Main recommendations**

21. Tobacco-related biomarkers can be used to measure the chemical content of tobacco and emissions exposure or the potential or actual biological harm to the human body as a consequence of such exposure. Genetic biomarkers can indicate disease susceptibility in smokers. Although there are as yet no biomarkers, or panels of biomarkers that are sufficiently robust to support a risk-or harm-reduction claim in a regulatory setting, biomarkers have substantive value in some regulatory contexts. Exposure biomarkers should be required in studies submitted for regulatory approval of claims regarding tobacco-use cessation interventions; in support of exposure-reduction claims; in studies defining the addictiveness of different products; and can be useful in evaluating or monitoring the effectiveness of individual-level tobacco cessation interventions.

### **Significance for public health policies**

22. Self-reporting smoking status and daily cigarette consumption remain the recommended methods for quantifying and identifying trends in tobacco exposure in the general population, and both methods have been validated in epidemiological studies as predictors of disease outcomes. However, differences in cigarette design and variations in individual smokers' patterns of use limit the accuracy of self reporting as a method of assessing the exposure received by individuals from the use of different tobacco products. Biomarkers offer the potential to quantify more accurately individual

exposure to nicotine and other specific tobacco emissions, and are valuable in situations where increased accuracy in defining smoking status or more precise measurements of intensity of exposure are needed. Care needs to be taken in extrapolating from the biomarker measurement of exposure to one tobacco-smoke constituent either to whole-smoke exposure or to disease risk when comparing exposure levels from different tobacco products.

23. Exposure biomarkers are also useful in evaluating specific public policy questions about the effect of policy changes on exposures in the general population, notably whether restrictions on smoking in general or in specific locations reduce exposure.

### **Implication for the Organization's programmes**

24. In this area of tobacco control, WHO should take the lead in promoting and supporting research on biomarkers of tobacco exposure and tobacco-induced harm.

### **Setting maximum limits for *N*-nitrosonornicotine and 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone in cigarette smoke**

#### **Main recommendations**

25. Smoke emissions contain many potent toxicants, whose relative amounts per mg nicotine vary substantially across existing brands. It is not possible to eliminate all these toxicants or to estimate with any reliability the risk reductions that would result from reducing the level of a single toxicant, but reducing the amount of toxicants in smoke to the extent possible is, from a public health perspective, a worthwhile and reasonable regulatory goal. This approach is similar to that of reducing the concentrations of contaminants in food products in the absence of clear evidence that measurably alters the disease risks. From a public health perspective, it is difficult to justify allowing high levels of carcinogens in some cigarette brands when other brands contain only a fraction of those levels, despite the uncertainty about the benefit to be gained by reducing a single constituent.

26. The question whether setting maximum limits for some potent smoke toxicants could reduce the toxicant levels produced by cigarette brands within a given market is being examined. It is proposed that, initially, maximum limits should be set for the carcinogenic tobacco-specific nitrosamines *N*-nitrosonornicotine and 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone.

27. Setting a maximum level for these nitrosamines at the midpoint of the wide range across brands would substantially lower the levels for the brands remaining on the market. There is evidence that their concentrations in tobacco can readily be lowered by changes in curing and other processes, which suggests that tobacco manufacturers could easily reduce the levels for all brands to below the maximum recommended levels within a short time. The Study Group recommended that, after an appropriate reporting interval, the import, export, distribution and sale of brands with levels exceeding these maximum limits should be prohibited.

#### **Significance for public health policies**

28. Partly because of the high toxic effects of smoking, cigarettes have so far escaped effective product regulation. Adoption of the proposed maximum limits, banning brands exceeding those limits, and prohibiting claims based on meeting the limits would allow regulation of tobacco emissions and a lowering of the concentrations of toxicants in the smoke of the remaining brands without misleading the public about the relative risk of smoking different brands. This regulatory approach is directed at

manufacturers: it will encourage them to reduce the toxicants in their products to the maximum extent possible, and thus, it is a strategy for product regulation rather than harm reduction. It is suggested that WHO should recommend maximum limit values.

29. Maximum limits for a more complete list of constituents are being worked out as a next step. This list will include constituents that are thought to contribute to chronic lung disease and cardiovascular disease, as well as to cancer.

30. Since measurements by machine testing, notably for tar and nicotine, have been misrepresented to consumers as indicating differences in exposure or risk, marketing claims by manufacturers, the ranking of brands within a market, and decisions by consumers concerned about their disease risks should not be based on the values determined by such methods.

### **Implications for the Organization's programmes**

31. As the capacity of the tobacco manufacturers to achieve lower levels of toxicants in cigarettes increases, maximum levels can gradually be lowered to ensure that the toxicant yields are progressively reduced to a minimum. It is expected that most countries will require tobacco contents and emissions testing to be carried out by the tobacco manufacturers, with periodic validation by independent laboratories competent in the analysis of tobacco constituents, such as those belonging to the WHO Tobacco Laboratory Network. If the Network is to succeed in counterbalancing the industry's tobacco testing and research capability, it needs the continued support of WHO. It is only through a comprehensive understanding of the characteristics of tobacco products, including their contents, emissions, and design features, that public health authorities and regulatory agencies will be in a position to regulate effectively these products.

## **WHO EXPERT COMMITTEE ON PROBLEMS RELATED TO ALCOHOL CONSUMPTION**

### **Second report<sup>1</sup>**

**Geneva, 10–13 October 2006**

### **Main recommendations**

32. The Committee reviewed the health and social consequences of alcohol consumption and disease burden attributable to alcohol in the context of mechanisms of alcohol-related harm and recent trends in alcohol consumption worldwide. After reviewing available evidence, including the latest data on the contribution of alcohol consumption to the global disease burden the Committee made several recommendations emphasizing WHO's role in coordinating a global response, and the need for global action to reduce alcohol-related harm through effective mechanisms for international action and country support.

33. The Committee also recommended a range of strategies and policy options that have a sound evidence base and global relevance for reducing alcohol-related harm, emphasizing that their adaptation and implementation at the national and sub-national levels should take into account specific

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<sup>1</sup> WHO Technical Report Series, No. 944, 2007.

cultural and legal contexts and the local configuration of alcohol problems. The Committee recommended that WHO should support governments, particularly in low- and middle-income countries, in developing, implementing and evaluating national and sub-national evidence-based policies, action plans and programmes.

34. In reviewing the disease burden attributable to alcohol worldwide, the Committee recommended that comparative assessment of alcohol as a risk factor to health should continue, and emphasized the need for a sustainable global information system on alcohol based on comparable data, agreed definitions, and country-based counterparts to monitor progress in reducing public health problems caused by harmful use of alcohol. The Committee also recommended that data on policies, laws, regulations and their effectiveness should be integrated into this information system and that practical experiences in the implementation of alcohol policies in different societies should be collated and disseminated.

### **Significance for public health policies**

35. The disease burden attributable to alcohol consumption is significant and, in many countries, public health problems caused by harmful use of alcohol represent a substantial health, social and economic burden. Reduction of the alcohol-attributable burden is becoming a priority area for international public health. Alcohol-related harm can be reduced through the implementation of proven alcohol strategies, including at the global level. The Committee's conclusions and recommendations have significant implications for future developments in this area.

36. Although substantial progress has been made in quantifying the disease burden attributable to alcohol, some areas of alcohol-related harm have not received sufficient attention at the global level. The Committee identified several priority areas for further work, including the measurement of alcohol-attributable social harm and contributions of harmful use of alcohol to infectious disease morbidity and mortality.

37. The Committee emphasized the important role of health workers in supporting and implementing effective public health policies and interventions for reducing alcohol-related harm, within and outside the health sector, and recommended several strategies and programmes for further support and development.

38. As the formulation and implementation of alcohol policies involves sectors other than health, collaboration between different national and international agencies and organizations is necessary in tackling public health problems caused by harmful use of alcohol. An example of this would be the need to assess the potential implications of trade and trade agreements for alcohol policies and alcohol-related harm.

### **Implications for the Organization's programmes**

39. Resolution WHA58.26 on Public health problems caused by harmful use of alcohol requests the Director-General to draw up recommendations for effective policies and interventions to reduce alcohol-related harm. The conclusions and recommendations of the Expert Committee will be used by WHO in preparing recommendations and programme activities at the global and regional levels to reduce the disease burden attributable to alcohol consumption worldwide.

40. WHO should continue and strengthen its support to low- and middle-income countries in implementing, evaluating and monitoring alcohol policies. A framework of regional and global

supporting mechanisms should be developed in consultation with Member States, international organizations and other relevant stakeholders.

41. The global information system on alcohol and public health, to be based on the WHO Global Alcohol Database, regional information systems on alcohol and regular reports from Member States, as recommended by the Expert Committee, will enable the Organization to monitor progress in reducing the public health problems attributable to alcohol worldwide and to disseminate information on the implementation and effectiveness of alcohol strategies and interventions in different societies and settings.

42. Implementation of strategies to reduce public health problems caused by harmful use of alcohol requires coordination with different programmes within and outside the Organization and increased collaboration and interaction with other United Nations agencies, international organizations, nongovernmental organizations and other stakeholders. This may require appropriate coordination mechanisms.

43. WHO will continue its interaction with trade, hospitality and alcohol-industry sectors in order to encourage implementation of strategies and interventions in the areas of production, distribution and marketing of alcoholic beverages. Concerns regarding the potential implications of the international alcoholic-beverages trade and trade agreements for alcohol-related harm and alcohol policies will be addressed by the Secretariat within the framework of resolution WHA59.26 on International trade and health.

## **WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS**

### **Forty-first report<sup>1</sup>**

**Geneva, 16-20 October 2006**

#### **Main recommendations**

44. The WHO Expert Committee on Specifications for Pharmaceutical Preparations reviews developments in quality assurance of medicines and coordinates activities leading to the adoption of recommendations and the provision of tools to assure the quality of medicines and their starting materials. It draws up quality-control specifications and determines International Chemical Reference Substances focusing on essential medicines and medicines used in the treatment of large populations for which international quality requirements are not generally available.

45. During this Expert Committee meeting, three guidelines relating to the prequalification of priority medicines and of quality-control laboratories were adopted, including the procedures for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies, and for assessing the acceptability, in principle, of quality-control laboratories for use by United Nations agencies, and guidance on variations to a prequalified product dossier.

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<sup>1</sup> WHO Technical Report Series, No. 943, 2007.



46. Twelve monographs for antiretroviral agents, including fixed-dose combinations (abacavir oral solution; abacavir sulfate tablets; didanosine tablets; didanosine oral solution (adult formulation); lamivudine oral solution; lamivudine tablets; stavudine capsules; zidovudine capsules; zidovudine intravenous injection; zidovudine oral solution; zidovudine and lamivudine tablets; zidovudine, lamivudine and abacavir tablets) and four for antimalarial medicines (doxycycline hyclate capsules; doxycycline hyclate tablets; doxycycline hyclate; lumefantrine) were adopted, together with four new International Chemical Reference Substances (didanosine; didanosine for system suitability; efavirenz; and nevirapine) and a policy statement on related substance testing in monographs for dosage forms. The general guidelines for the establishment, maintenance and distribution of chemical reference substances were revised to provide better guidance on secondary reference standards.

47. The following new standards and guidelines were adopted and recommended for use: The International Pharmacopoeia. Related substances tests: dosage form monographs; list of available International Chemical Reference Substances; general guidelines for the establishment, maintenance and distribution of chemical reference substances; procedure for assessing the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies (update); procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (update); and guidance on variations to a prequalified product dossier.

### **Significance for public health policies**

48. The advice and recommendations provided by the Expert Committee and published by WHO are intended to help national and regional authorities (in particular drug regulatory authorities), United Nations organizations such as UNICEF, procurement agencies, major international bodies and institutions, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, to combat problems of counterfeit and substandard medicines. WHO's international standards are used to calibrate regional, national or manufacturers' standards.

49. The international guidelines, specifications and nomenclature produced by this Expert Committee serve – without always being in the headlines – all Member States, international organizations, United Nations agencies, and regional and interregional harmonization efforts, and underpin important global initiatives. The aim is to provide technical and independent advice on quality assurance for essential medicines and for medicines used in the treatment of large populations for which international quality requirements are not generally available. The nomenclature, International Nonproprietary Names for pharmaceutical substances, is used – directly or indirectly – by everyone working with medicines.

50. Quality of medicines is all too often taken for granted. Patients' health should not be compromised through the use of poor-quality medicines, nor should public or private resources be wasted on medicines that might be ineffective or even harmful.

### **Implications for the Organization's programmes**

51. The Expert Committee provides up-to-date recommendations on the quality of medicines. Its work enables WHO to fulfill its constitutional responsibilities in this area. Its observations, conclusions and recommendations have significant implications for numerous WHO activities. In particular, they provide timely recommendations, reference standards and tools to assure the quality of medicines. The global norms and standards defined by the Committee are used by programmes such as the Global Malaria Programme, the HIV/AIDS Programme, and by partnerships such as Stop TB and the International Medical Products Anti-Counterfeiting Taskforce.

52. The Prequalification programme could not function without the guidelines, standards, specifications and new guidance texts adopted by this Committee after the usual, rigorous consultative process. In turn, the Prequalification programme provides valuable feedback to the Expert Committee and gives staff from the drug regulatory authorities practical experience in joint inspections and joint regulatory assessment activities with the participation both of developed and developing countries. This practical experience is later passed on through training workshops.

53. Based on the Expert Committee's recommendations, WHO will continue to promote implementation of quality-assurance tools and systems for medicines both within and outside the Organization. It will also lead and coordinate international efforts to define and harmonize clear, independent and practical standards and guidelines for medicines in view of increasing globalization and its related challenges, which can no longer be tackled solely at the national level.

54. WHO will make good use of all its resources to ensure that patients have access to good-quality medicines when they need them. The Secretariat's first objective must be to assist Member States and other parties involved in the supply of medicines, by providing tools that will help to ensure the safety, efficacy and quality of medicinal products.

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