DIETARY EXPOSURE ASSESSMENT OF CHEMICALS IN FOOD

Natalija Vragović
Center for Food Control, Zagreb, Croatia

Keywords: Chemical contaminants, dietary exposure, food consumption, risk assessment.

Contents

Summary

The contamination of food by chemical hazards is a worldwide public health concern and is a leading cause of trade problems internationally. Contamination may occur through environmental pollution of the air, water and soil, such as the case with toxic metals, PCBs and dioxins, or through the intentional use of various chemicals, such as veterinary drugs, pesticides and other agrochemicals. Food additives and contaminants resulting from food manufacturing and processing can also adversely affect health. Scientists and public-health agencies have developed risk assessment methods to derive human safe levels of exposure. Risk assessment has been divided into four sequential steps: hazard identification, hazard characterization, exposure assessment and risk characterization.

Dietary exposure assessment is a crucial component of risk assessment applied to chemical substances in foods and beverages. In order to calculate reliable estimates of

the amounts ingested through the diet for a specific chemical substance, three elements have to be taken into account: levels and fate of the chemical in food; food consumption patterns and integration of these elements to determine exposure. In all areas the limitations of the approaches currently used lead to uncertainties that can either cause over- or underestimation of real intakes and thus of risk.

1. Introduction

There are different views on usefulness and adequacy of individual animal and plant species as a source of food and these opinions are changing under the influence of scientific knowledge, production conditions, possibility of breeding of individual animal species, economical potential of individuals or community, religions, habits and even prejudices.

Harmful residues in food include a series of chemical compounds, which could be different food additives, processing aids, pesticides, polychlorinated biphenyls, nitrates and nitrites, heavy metals, mycotoxins, and in food of animal origin also veterinary-medicinal products. Food-borne disease remains a real and formidable problem in both developed and developing countries, causing great human suffering and significant economic losses. Up to one third of the population of developed countries may be affected by food-borne diseases each year, and the problem is likely to be even more widespread in developing countries, where food and water-borne diarrheal diseases kill an estimated 2.2 million people each year, most of them children. Chemical hazards in foods occasionally cause acute illnesses, and some food additives, residues of pesticides and veterinary drugs and environmental contaminants may pose risks of long-term adverse effects on public health. New technologies such as genetic modification of agricultural crops have raised additional food safety concerns. In order to reduce those negative trends, international organizations like Food and Agriculture Organization of the United Nations, World Health Organization, Codex Alimentarius and World Organisation for Animal Health are involved with numerous activities in this field. A key discipline for further reducing food-borne illness and strengthening food safety systems is risk analysis, a systematic, disciplined approach for making food safety decisions developed primarily in the last two decades, includes three major components: risk assessment, risk management and risk communication. Risk assessment at the international level provides the scientific basis for the establishment of Codex standards, guidelines, and other recommendations and includes dietary exposure assessments as an essential component. The role of dietary exposure assessments has grown significantly in light of the World Trade Organization's "Agreement on the Application of Sanitary and Phytosanitary Measures". Paragraph 16 of this agreement requires that sanitary and phytosanitary measures be based on sound scientific risk assessment. The agreement also states that sanitary measures that are consistent with standards, guidelines, and recommendations of the Codex Alimentarius Commission are considered to comply with the requirements of the agreement.

Dietary exposure assessments combine food consumption data with data on the concentration of chemicals in food. The resulting dietary exposure estimate is then compared with the relevant toxicological or nutritional reference value. Assessments may be undertaken for acute (short-term) or chronic (long-term) exposures, where acute exposure covers a period of 24 h and long-term exposure covers average daily exposure over the entire lifetime. Dietary exposure assessments of nutrients use default assumptions that tend to underestimate exposure, whereas dietary exposure assessments of potentially toxic food chemicals use default assumptions that tend to overestimate exposure. For some nutrients, two assessments may be necessary because of the specific need to look at both nutrient adequacy and the potential to exceed upper safety levels. Ideally, dietary exposure to hazardous substances can be assessed by combining data on concentration in all food products with data on their consumption. However, it is considered to be neither cost-effective nor necessary to collect detailed data for every substance, and a stepwise procedure is commonly used to focus resources on the most important issues. Screening methods, designed to look for 'worst case' situations, are first used to target chemicals that might be of health concern for the general population or for certain at-risk groups. The quality of the dietary exposure assessments not only depends on the quality of the data collected, but also on the integration tools used for initial screening or for the eventual more precise estimations.

2. Role of Risk Assessment

The first risk analysis paradigm for public health was proposed by the U.S. National Academy of Sciences - NAS and focused on assessing the risk of cancer from chemicals in food.

Figure 1: The risk analysis paradigm

Risk assessment is the central component of risk analysis and provides a scientific basis for risk management decisions on measures that may be needed to protect human health. Risk assessment consisting identification of the agent causing adverse health effects (hazard identification), evaluation of the intake of the agent (exposure assessment), evaluation of the nature of the adverse health effects (hazard characterization), and estimation of occurrence and severity of the adverse health effects (risk characterization).

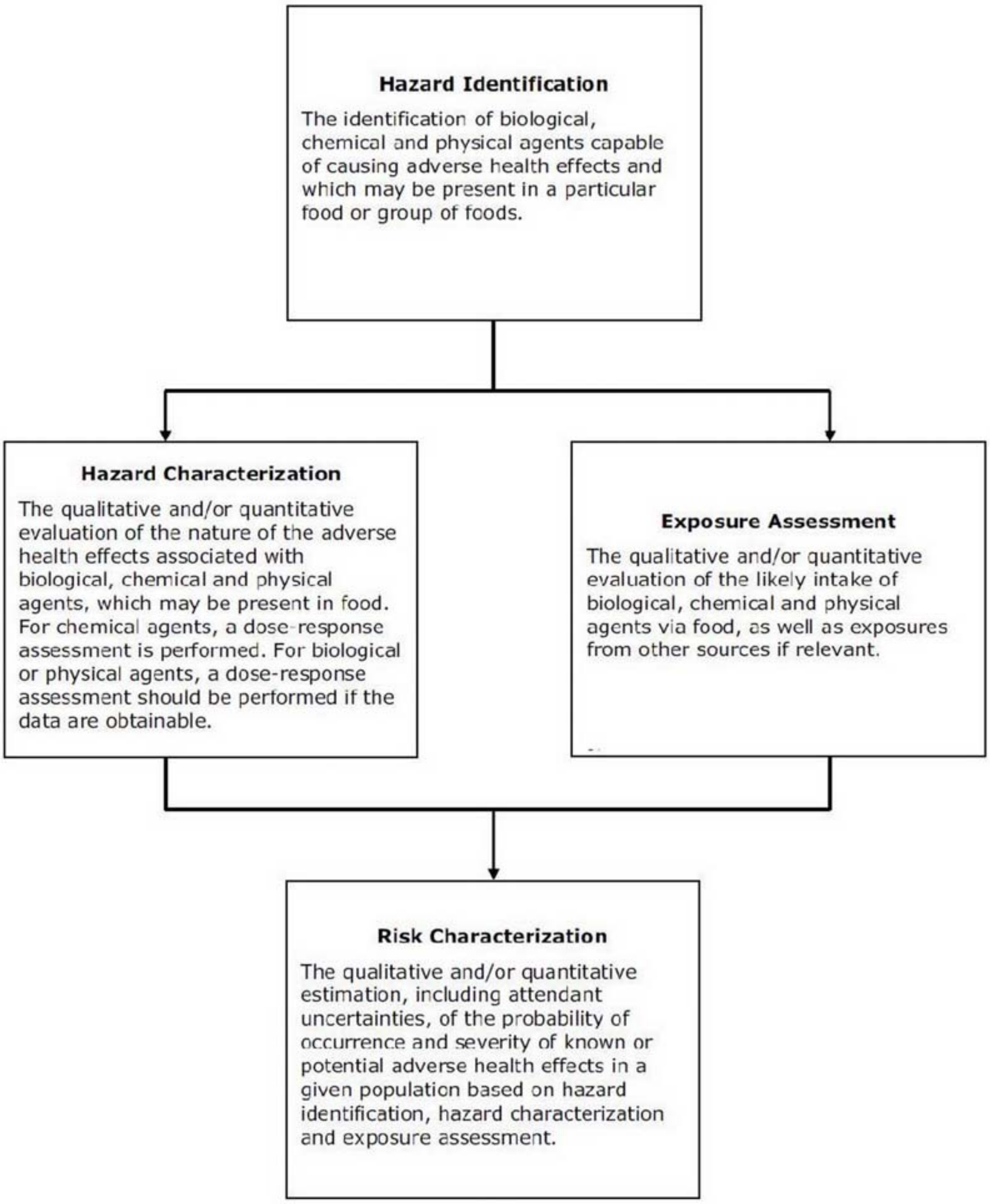

Figure 2: Generic Codex description of the components of risk assessment

It is a conceptual framework that, in the context of food chemical safety, provides a mechanism for the structured review of information relevant to assessing possible health outcomes in relation to exposures to chemicals present in food. The risk assessment is used to develop and evaluate risk management strategies, such as introducing measures to control the use or release of the chemical, restricting human contact, or introducing compliance testing or surveillance.

Risk management is process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.

The functional separation of risk assessment from risk management helps assure that the risk assessment process is unbiased. However, certain interactions are needed for a comprehensive and systematic risk assessment process. The relationship between risk assessment and risk management is an interactive, often iterative, process.

Risk communication is an integral part of risk analysis and helps to provide timely, relevant and accurate information to, and to obtain information from, members of the risk analysis team and external stakeholders, in order to improve knowledge about the nature and effects of a specific food safety risk assessment. It contributes to transparency of the risk analysis process and promotes broader understanding and acceptance of risk management decision.

Risk assessment of chemical substances present in or on food forms the core work of Joint FAO/WHO Expert Committee on Food Additives (JECFA) and Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Based on the advice from these two committees, food safety measures are taken in the risk management executed by countries nationally and by the Codex Alimentarius Commission (CAC) internationally. Whereas JECFA and JMPR base their evaluations on scientific principles and ensure necessary consistency in their risk assessment determinations, CAC and its respective committees that deal with chemicals in food are responsible, as risk managers, for the final decisions on establishing maximum limits for pesticide residues, veterinary drug residues, contaminants and additives in food and adopting other related measures.

2.1. Hazard Identification

Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment. Hazard identification is defined as the identification of biological, chemical and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods.

The purpose of food chemical hazard identification is to evaluate the weight of evidence for adverse health effects, based on assessment of all available data on toxicity and mode of action. It is designed to primarily address two questions:

1) the nature of any health hazard to humans that an agent may pose and
2) the circumstances under which an identified hazard may be expressed.

Hazard identification is based on analyzes of a variety of data, ranging from observations in humans or domestic animals and studies in laboratory animals and *in vitro* laboratory studies through to analysis of structure–activity relationships. From the range of studies and observations available, the nature of any toxicity or adverse health effects occurring and the affected target organs or target tissues are identified.

2.2. Hazard Characterization

Hazard characterization is defined as the qualitative and, wherever possible, quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents, which may be present in food. For chemical agents, a dose–response assessment is performed.

Hazard characterization describes the relationship between the administered dose of, or exposure to, a chemical and the incidence of an adverse health effect. The critical effect - that is, the first adverse effect observed as the dose or exposure is increased is determined. In cases where the toxic effect is assumed to have a threshold, hazard characterization usually results in the establishment of healthbased guidance values for example, an acceptable daily intake (ADI) for additives or residues of pesticides or veterinary drugs, or a tolerable intake (TI) for contaminants. For some substances used as food additives, the ADI may not need to be specified; in other words, no numerical ADI is considered necessary. This may be the case when a substance is assessed to be of very low toxicity, based on the biological and toxicological data, and the total dietary intake of the substance, arising from the levels used in foods to achieve the desired function, does not represent a hazard.

2.3. Exposure Assessment

The Codex Alimentarius Commission's Procedural Manual defines exposure assessment as "the qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant".

In the case of food chemicals, dietary exposure assessment takes into consideration the occurrence and concentrations of the chemical in the diet, the consumption patterns of the foods containing the chemical and the likelihood of consumers eating large amounts of the foods and of the chemical being present in these foods at high levels. Usually a range of intake or exposure estimates will be provided (e.g. for average consumers), and estimates may be broken down by subgroup of the population (e.g. infants, children, adults).

Estimates of dietary intakes of food additives, residues of pesticides and veterinary drugs and contaminants require information on the consumption of relevant foods and the concentrations of the chemical of interest in those foods. In general, three approaches are available in exposure assessment:

1) total diet studies;
2) selective studies of individual foods, and;
3) duplicate portion studies.

Guidelines for the study of dietary intakes of chemical contaminants are available from WHO (1985). The GEMS/Food international databases include several important streams of data related to food contamination and food consumption:

- The level of chemicals is measured in raw food commodities as well as in food as consumed by final consumer.
- A list of the WHO 13 cluster diets that have been created to cover the average food consumption in 13 regions of the world. These levels of consumption are used to serve as a basis for assessing the exposure to chemical contaminants from food, but can also be used for other purposes like nutritional evaluation.

GEMS/Food currently maintains a database of five regional diets as well as a composite "global" diet. Daily dietary intakes of nearly 250 individual primary and semi-processed food commodities are available. The African, Asian, East Mediterranean, European and Latin American regional diets are based on selected national data from FAO Food Balance Sheets. Consumption data derived using this approach provide no information on extreme consumers.

Dietary intake determinations can be relatively straight-forward for additives, pesticides and veterinary drugs as the relevant foods and their use levels are specified by their approved conditions of use. However, the actual levels of additives and residues of pesticides and veterinary drugs present in foods are often well below the maximum levels permitted. In regard to residues of pesticides and veterinary drugs, levels on or in food are often totally absent because only a portion of the crop and animal population is usually treated or as consequences of withdrawal period.

Data on the levels of food additives in foodstuffs can be obtained from the manufacturers. The dietary intake of contaminants requires information on their distribution in foods that can only be obtained by analyzing representative samples of foods with sufficiently sensitive and reliable analytical methods. Maximum Residue Limits (MRLs) for pesticides and veterinary drugs and Maximum Levels for additives can be established from their conditions of use. In the simplest case, a food additive used at a specific level would be stable in the food until consumption. The Maximum Level would then equal the intake level. However, in many cases, the amount of the chemical of interest may change prior to consumption. For example, food additives may degrade during storage or react with the food. Pesticide residues in raw agricultural products may degrade/accumulate during further processing. The fate of veterinary drug residues in food products is influenced by metabolism, kinetics, distribution and withdrawal periods required for treated animals.

The establishment of MRLs must take into account any changes in the nature or level of the residue that may occur prior to a commodity entering commerce or that may occur under any anticipated conditions of subsequent use. Contaminants have no intended tehnological effect in the food and guideline levels are usually set as low as reasonably achievable.

The theoretical total dietary intake of additives, pesticides and veterinary drugs must be below their corresponding ADIs. Setting guideline levels for contaminants present special problems. There is usually a paucity of data to establish a provisional tolerable intake. On occasion, the levels of the contaminants are higher than what an established provisional tolerable intake would permit. In these cases, the guideline levels are set on economic and/or technical considerations.

Within the Codex Alimentarius Commission, the chemical contamination of food is addressed by the Codex Committee on Food Additives and Contaminants (CCFAC) and the Codex Committee on Pesticide Residues (CCPR). Risk management decisions are highly dependent on comparable and reliable exposure assessments and GEMS/Food has provided assistance on a range of chemical issues to CCFAC and CCPR as well as to their scientific advisory bodies, namely JECFA and JMPR.

Reliable food intake data are essential for exposure assessments based on measuring levels of chemical agents in food. Detailed food consumption data for the average consumer as well as for different population groups are important for assessing exposure, particularly by sensitive groups. In addition, comparable food consumption data, particularly with respect to staple foods from different regions of the world are essential for developing an international risk assessment approach to food safety.

-
-
-

Bibliography

Albero B., Sa´nchez-Brunete C., Tadeo J.L. (2005). Multiresidue determination of pesticides injuice by solid-phase extraction and gas chromatography–mass spectrometry. *Talanta* **66**, 917–924. [In this paper the method for the simultaneous determination of 50 pesticides in commercial juices are estimated].

Arcella D., Soggiu M.E., Leclercq C. (2003). Probabilistic modelling of human exposure to intense sweeteners in Italian teenagers: validation and sensitivity analysis of a probabilistic model including indicators of market share and brand loyalty. *Food Additives and Contaminants* **20**(Suppl.), 73–86. [This paper presents validation and sensitivity analysis of a probabilistic model including indicators of market share and brand loyalty].

Brady M.S., Katz S.E. (1988). Antibiotic/antimicrobial residues in milk. *Journal of Food Protection* **51**, 8–11. [This presents a method to evaluate antibiotic and antimicrobial residues in milk].

Burchat C.S., Ripley B.D., Leishman P.D., Ritcey G.M., Kakuda Y., Stephenson G.R. (1998). The distribution of nine pesticides between the juice and pulp of carrots and tomatoes after home processing. *Food Additives and Contaminants* **15** (1), 61–71. [In this paper relationship between the pulp/juice distribution and water solubility of the pesticide are estimated].

Cadby P. (1996). Estimating intakes of flavouring substances. *Food Additives and Contaminants* **13**(4), 453– 460. [It is shown that washing of the produce removed more residue from carrots than from tomatoes, but it did not affect the relative distribution of the residues].

Carter R.L., Sharaugh C.O., Stapell C.A. (1981). Reliability and validity of the 24-hour recall. *Journal of the American Dietetic Association* **79**, 542–547. [It is shown that nutrient intakes derived from 24-h recalls tend to underestimate true intakes of some macronutrients for some subjects].

Codex Alimentarius Commission. European Commission (1998). Report on methodologies for the monitoring of food additive intake across the European Union. Final report submitted by the Task Co-ordinator, 16 January 1998. Report of a Working Group on scientific co-operation on questions relating to food. Brussels, Belgium, European Commission Directorate General III Industry (Task 4.2; SCOOP/INT/REPORT/2). [This is report on methodologies for the monitoring of food additive intake].

Codex Alimentarius Commission (2003). Revised guidelines on Good Laboratory Practice in residue analysis. Rome, Italy, Food and Agriculture Organization of the United Nations, Joint FAO/WHO Food Standards Programme (http://www.codexalimentarius.net/download/standards/378/cxg_040e.pdf). [These guidelines define such good analytical practice and may be considered in three inter-related parts: The Analyst; Basic Resources; The Analysis].

Codex Alimentarius Commission (2010). Pesticide residues in food. Rome: FAO/WHO Food Standard. (http://www.codexalimentarius.net/mrls/pestdes/jsp/pest_q-e.jsp). [This document contains summaries of the residues data considered, together with the recommendations made].

Codex General Standard for Contaminants and Toxins in Foods. CODEX STAN 193-1995. [This Standard contains the main principles and procedures which are used and recommended by the Codex Alimentarius in dealing with contaminants and toxins in foods and feeds, and lists the maximum levels of contaminants and natural toxicants in foods and feeds which are recommended by the CAC to be applied to commodities moving in international trade].

Commission Regulation (EC) 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. L364/5-24. [This Regulation setting maximum levels for certain contaminants in foodstuffs].

Commission Directive 2002/63/EC of 11 July 2002 establishing community methods of sampling for the official control of pesticide residues in and on products of plant and animal origin and repealing Directive 79/700/EEC. L187/30-43. [This Directive apply to the sampling of products of plant and animal origin in order to determine the level of pesticide residues for the purposes of Directives 76/895/EEC, 86/362/EEC, 86/363/EEC and 90/642/EEC].

Commission Regulation (EC) 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. 2005R0396-EN-10.04.2008-002.001, 2–46. [This Directive relating to the fixing of maximum levels for pesticides in or on food and feed of plant and animal origin].

Commission Regulation (EC) 178/2006 of 1 February 2006 amending Regulation (EC) No. 396/2005 of the European Parliament and of the Council to establish Annex I listing the food and feed products to which maximum levels for pesticide residues apply. L29/3-25. [The text in the Annex to this Regulation is added as Annex I to Regulation (EC) No 396/2005].

Commission Regulation (EC) 839/2008 of 31 July 2008 amending Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards Annexes II, III and IV on maximum residue levels of pesticides in or on certain products. [The Annexes to Regulation (EC) No 396/2005 are amended in accordance with the Annex to this Regulation].

Council Directive 91/414/EEC (1991) concerning the placing of plant protection products on the market. Official Journal of the European Communities, L230, 1– 32 (modified: Official Journal of the European Communities, L170 (25 June 1992), 40). [The Directive and its six Annexes set out common rules and guidance on data requirements, data evaluation, risk assessment; the transition from a national to the EU authorisation system, the protection of commercial information (data protection); and public access to information on pesticides].

Droppers W.F.G.L. (2006). OIE philosophy, policy and procedures for the development of food safety standards *Revue Scientifique et Technique OIE* 2006, **25** (2), 805-812. [This work reviews OIE philosophy, policy and procedures for the development of food safety standards].

Currie D., Lynas L., Kennedy G., Mc Caughey J., (1998). Evaluation of modified EC four plate method to detect antimicrobial drugs. *Food Additives and Contaminants* **5**, 651–660. [This paper describes a modification of the EC Four Plate Method based on microbial growth inhibition of Bacillus subtilis].

Dewdney J.M., Maes L., Raynaud J.P., Blanc F., Scheid J.P., Jackson T., Lens S., Verschueren C., (1991). Risk assessment of antibiotic residues of β-lactams and macrolides in food products with regard to their immuno-allergic potential. *Food and Chemical Toxycology* **29**, 477-483. [This review assesses the potential risk of such reactions in general, but focuses on allergy to penicillin and macrolide residues in particular].

Egmond H.J., Nouws J.F.M., Schilt R., van Lankveld-Driessen W.D.M., Streut-jens-van Neer, E.P.M:, Simons F.G:H. (2000). Stability of antibiotics in meat during a simulated high temperature destruction process. State Institute for Quality Control of Agricultural Products (RIKILT), Bornsesteeg 45, NL- 6708 PD Wageningen, The Netherlands. [In this paper with a simulation model at laboratory-scale, the stability of sixteen antibiotics during the destruction process of animal and offal's was investigated].

European Agency for the Evaluation of Medicinal Products (1999). Antibiotic resistance in the European Union associated with the therapeutic use of veterinary medicines. Report No. EMEA/CVMP/342/99-Final, The European Agency for the Evaluation of Medicinal Products (EMEA), London. [A study on investigation the prevalence and changes in antibiotic resistance in animals, its effect on therapy and potential risk to human health].

European Food Safety Authority (2005). Opinion of the Scientific Committee on a request from EFSA related to Exposure Assessment. (http://www.efsa.europa.eu/etc/medialib/efsa/science/sc_commitee/sc_opinions/ 1028.Par.0001.File.dat/sc_op_ej249_exposure_en2.pdf). [The Scientific Committee is of the opinion that, in principle, substances which are both genotoxic and carcinogenic should not be deliberately added to food and feed at any point in the food chain. The same also applies for substances which may leave residues that could have both genotoxic and carcinogenic properties (e.g. pesticides)].

European Food Safety Authority (2006). Guidance of the Scientific Committee on a request from EFSA related to Uncertainties in Dietary Exposure Assessment. EFSA Journal, 438, 1-54. (www.efsa.europa.eu). [This opinion has been produced with the aim of improving and harmonising the treatment of uncertainty in dietary exposure assessment. The opinion reviews the types of uncertainties that may affect dietary exposure assessment].

FAO (2002). Submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed, 1st ed. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper, No. 170) (http://www.fao.org/ag/agp/agpp/pesticid/JMPR/Download/FAOM2002.pdf). [The Manual gives the historical background of the operation of the JMPR and describes the object of the work, the procedures involved in selection of compounds, the data requirements for estimating maximum residue levels and the principles followed in the evaluation of experimental results and information provided].

FAO (2003). Assuring food safety and quality. Guidelines for strengthening national food control systems. FAO Food and Nutrition Paper No. 76 (http://ftp.fao.org/docrep/fao/006/y8705e/y8705e00.pdf). [This paper was prepared to enable national authorities, particularly in developing countries, to improve their food control systems].

FAO (2009). Residue evaluation of certain veterinary drugs. Rome, Food and Agriculture Organization of the United Nations, pp 1–28 (FAO JECFA Monographs, No. 6) (http://www.fao.org/docrep/011/i0659e/i0659e00.htm). [This monographs provided the scientific basis for the recommendations of MRLs].

FAO/WHO (1997). Food consumption and exposure assessment of chemicals. Report of an FAO/WHO Consultation on Food Consumption and Exposure Assessment of Chemicals, Geneva, 10–14 February 1997. Geneva, World Health Organization (WHO/FSF/FOS/97.5). [The Consultation recommended an expansion of the five regional diets; considered various issues related to acute dietary exposure assessments; made recommendations to ensure that the overall approach to international dietary exposure assessments is rational, consistent across different Codex committees, and uses the best available food consumption or residue data with the most appropriate method for combining the two data sets].

FAO/WHO (2000). The Interaction between assessors and managers of microbiological hazards in food. Report of a WHO Expert Consultation in collaboration with the Institute for Hygiene and Food Safety of the Federal Dairy Research Centre, Germany and the Food and Agriculture Organization of the United Nations (FAO). Kiel, Germany, 21-23 March 2000. [This report is a elaboration of the risk analysis process].

FAO/WHO (2001). Guidelines for the preparation of working papers on intake of food additives for the Joint FAO/WHO Expert Committee on Food Additives. Rome, Food and Agriculture Organization of the United Nations; Geneva, World Health Organization (http://www.who.int/ipcs/food/jecfa/en/intake_guidelines.pdf). [These notes are designed to guide authors in the preparation of working papers on the intake of food additives for the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Such working papers summarize the available information on food consumption and levels of food additives in processed foods and provide estimates of intake on the basis of this information].

FAO/WHO Expert Committee on Food Additives (2005a): Dietary exposure assessment of chemicals in food, Annapolis, Maryland, USA. [This work presents the basic general principles and considerations when undertaking dietary exposure assessments].

FAO/WHO (2005b). Joint FAO/WHO Meeting on Pesticide Specifications. In: Pesticide residues in food—2005. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. Rome, Food and

Agriculture Organization of the United Nations, pp 33–34 (FAO Plant Production and Protection Paper, No. 183 (http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/2005_rep/report2005jmpr.pdf). [This project was test whether national and regional evaluations of toxicology and pesticide residues could be used as a basis for the JMPR evaluations].

FAO/WHO (2005c). Definition of fat-soluble pesticides in meat and fat. In: Pesticide residues in food—2005. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. Rome, Food and Agriculture Organization of the United Nations, pp 27–31 (FAO Plant Production and Protection Paper, No. 183 (http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/2005_rep/report2005jmpr.pdf). [This work revisit the criteria that are important when designing a residue as 'fat-soluble'].

FAO/WHO (2006a): Updating the Principles and Methods of Risk Assessment: MRLs for Pesticides and Veterinary Drugs, Rome. [This paper describes the basic principles applied in the risk assessment].

FAO/WHO (2006b). Food safety risk analysis: a guide for national food safety authorities. Rome, Food and Agriculture Organization of the United Nations and World Health Organization (FAO Food and Nutrition Paper, No. 87; (http://whqlibdoc.who.int/publications/2006/9789251056042_eng.pdf). [The Guide provides essential background information, guidance and practical examples of ways to apply food safety risk analysis].

FAO/WHO (2006c). Manual on development and use of FAO and WHO specifications for pesticides. March 2006 revision of the first edition. Rome, World Health Organization and Food and Agriculture Organization of the United Nations, Joint FAO/WHO Meeting on Pesticide Specifications (http://whqlibdoc.who.int/publications/2006/9251048576_eng_update_2006.pdf). [Manual describes development and use of FAO and WHO specifications for pesticides].

FAO/WHO (2006d). Evaluation of certain food contaminants. Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, World Health Organization (WHO Technical Report Series, No. 930) (http://whqlibdoc.who.int/ trs/WHO_TRS_930_eng.pdf). [This report represents the conclusions of a Joint FAO/WHO Expert Committee convened to evaluate the safety of various food contaminants, with the aim to advise on risk management options for the purpose of public health protection].

FAO/WHO (2008). Codex Alimentarius Commission procedural manual, 18th ed. Rome, Food and Agriculture Organization of the United Nations, Codex Alimentarius Commission (ftp://ftp.fao.org/codex/Publications/ProcManuals/Manual_18e.pdf). [The Procedural Manual of the Codex Alimentarius Commission describes the legal foundations and practical functioning of the Commission and its subsidiary bodies].

Fischer W.J., Tritscher A.M., Schilter B., Stadler R.H. (2003): Contaminants resulting from agricultural and dairy practices. In: Roginski H.: Encyclopedia of Dairy Sciences. Vol. 1. Elsevier Science, London: 516–525. [This paper focuses on the most important and most frequently used group of veterinary drugs].

GEMS/Food-Euro (1994). Workshop on reliable evaluation of low-level contamination of food. Kulmbach, Federal Republic of Germany, 3–5 March 1994 (EUR/ICP/EHAZ.94.12/WS03). [The recommended procedure ensures the reliability and comparability of GEMS/Food-EURO data sets and results in a more realistic description of the contamination of food].

GEMS/Food-Euro (1995). Second workshop on reliable evaluation of low-level contamination of food. Kulmbach, Federal Republic of Germany, 26–27 March 1995. EUR/ICP/EHAZ.94.12/WS04. (http://www.who.int/foodsafety/publications/chem/lowlevel_may1995/en/). [This paper reviews the nature and relevance of the factors affecting the collection of these two data sets and the procedures available for combining them to estimate consumer exposure. Considerable expertise and judgment are necessary to obtain an estimate of exposure that is robust enough for risk management purposes].

Gustafson R., Bowen R. (1997). Antibiotic use in animal agriculture. *Journal of Applied Microbiology* **83,** 531–541. [A review about antibiotic use in animal agriculture].

Halling-Sørensen B, Sengeløv G, Tjørnelund J (2002). Toxicity of tetracyclines and tetracycline degradation products to environmentally relevant bacteria, including selected tetracycline-resistant bacteria. *Archives of Environmental Contamination and Toxicology* **42**, 263-271. [Major degradation products formed due to the limited stability of parent tetracyclines (tetracycline, chlortetracycline, and oxytetracycline) in aqueous solution were theoretically identified at various environmental conditions, such as pH, presence of chelating metals, and light. Their potency was assessed on sludge bacteria, tetracycline-sensitive soil bacteria, and tetracycline-resistant strains.]

Hamscher G., Sczesny S., Hoper H. et al., (2002). Determination of persistent tetracycline residues in soil fertilized with liquid manure by high-performance liquid chromatography with electrospray ionization tandem mass spectrometry. *Analytical Chemistry* **74**, 1509–18. [In this paper a liquid chromatography/tandem mass spectrometry method was developed and employed to investigate in detail the distribution and persistence of the frequently used tetracyclines and tylosin in a field fertilized with liquid manure].

Hansen S.C. (1979). Conditions for use of food additives based on a budget method for an acceptable daily intake. *Journal of Food Protection* **42**, 429–434. [An evaluation of the budget method for screening food additive intake].

Hirs R., Ternes T., Haberer K., Kratz K.L. (1999). Occurrence of antibiotics on the aquatic environment. *Science of the Total Environment* 225, 109-118. [This article describes the analysis of various water samples for 18 antibiotic substances, from the classes of macrolid antibiotics, sulfonamides, penicillins and tetracyclines].

Institute for Environment and Health. (2004). Guidelines for good exposure assessment practice for human health effects of chemicals. Leicester, UK: University of Leicester. [The aim of this document is to provide guidance that will assist those having to undertake or evaluate exposure assessments].

IPCS (2004). IPCS risk assessment terminology. Geneva, Switzerland, World Health Organization, International Programme on Chemical Safety. Harmonization Project Document No. 1. (http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf) [The objective of this joint IPCS/OECD project is to develop internationally harmonized generic and technical terms used in chemical hazard/risk assessment, which will help facilitate the mutual use and acceptance of the assessment of chemicals between countries, saving resources for both governments and industry].

ISO (2005). General requirements for the competence of testing and calibration laboratories, 2nd ed. Geneva, International Organization for Standardization (ISO/IEC 17025:2005). [This International Standard specifies the general requirements for the competence to carry out tests and/or calibrations, including sampling. It covers testing and calibration performed using standard methods, non-standard methods, and laboratory-developed methods].

ISO (2008) Quality management systems—Requirements. Geneva, International Organization for Standardization (ISO 9001:2008). [ISO 9001:2008 is the internationally recognized quality management system that ensures a company's customers can count on a consistent level of quality products. The system documents all of the important steps needed to deliver that quality, from the initial design stage all the way through final delivery and support of the product. Regular re-certification by a qualified registrar ensures that the quality system remains in place and is effective].

Jørgensen S.E., Halling-Sørensen B. (2000). Editorial, "Drugs in the environment." *Chemosphere* **40**, 691–699. [Potential risks associated with releases of medicine into the environment have become an increasingly important issue. Bacterial resistance effect at low concentration of drugs may be irreversible].

Karvetti R.L., Knutts L.R. (1985). Validity of the 24-hour recall. *Journal of the American Dietetic Association* **85**, 1437–1442. [In this paper the validity of the 24-hour recall was studied with a comparison of recalled and observed food and nutrient intake. The observation was carried out during 1 day by recording the amounts of foods selected by the subjects at four meals].

Klein J., Alder L. (2003). Applicability of gradient liquid chromatography with tandem mass spectrometry to the simultaneous screening for about 100 pesticides in crops. *Journal of AOAC International* **86**, 1015–1037. [This work describes a generally applicable LC/MS-based multiresidue method for the determination of a large number of pesticides from distinct chemical classes after fast and inexpensive extraction and cleanup].

Kroes R., Muller D., Lambe J., Lowik M.R.H., van Klaveren J., Kleiner J., Massey R., Mayer S., Urieta I., Verger P., Visconti A. (2002). Assessment of intake from the diet. *Food and Chemical Toxycology* **40**

(2/3), 327-385. [The techniques used for the exposure assessment have been critically reviewed in this paper, to determine those areas where the current approaches provide a solid basis for assessments and those areas where improvements are needed or desirable].

Kühne M. Mitzscherling A.T. (2004). The entry of bound residues of tetracyclines into the food chain - a contribution to hazard identification. *Berliner und Munchener Tierarztliche Wochenschrift* **117**, 201-6. [This paper focuses on tetracycline residues in bones. Bones have been widely used as raw material for meat and bone meal and gelatine, and are also a frequent contamination of mechanical recovered meat. Bones contain tetracycline residues in concentrations up to 50 mg/kg].

Kümmerer K. (2003). Significance of antibiotics in the environment. *Journal of Antimicrobial Chemotherapy* **52**, 5-7. [This work describes the use of antibiotics and input into the environment; their fate in the environment; antimicrobial effects and the risk: assessment and management].

Lambe J. (2002). The use of food consumption data in assessments of exposure to food chemicals including the application of probabilistic modelling, Proceedings of the Symposium ''Nutritional aspects of food safety''. *Nutrition Society* **61**, 11-18. [Probabilistic analysis permits the exposure assessor to model the variability (true heterogeneity) and uncertainty (lack of knowledge) that may exist in the exposure variables, including food consumption data, and thus to examine the full distribution of possible resulting exposures. Challenges for probabilistic modeling include the selection of appropriate modes of inputting food consumption data into the models].

Lambe J., Cadby P., Gibney M. (2002a). Comparison of stochastic modeling to the intakes of intentionally added flavouring substances with theoretical added maximum daily intakes (TAMDI) and maximized survey-derived daily intakes (MSDI). *Food Additives and Contaminants*, **19**(1), 2-14. [Estimates of exposure to intentionally added flavoring substances based on two indirect methods, namely the theoretical added maximum daily intake (TAMDI) and maximized survey-derived daily intake (MSDI), were compared with exposure estimates based on a flavorings stochastic model (FSM). Twelve flavoring substances were chosen to reflect broadly the large number of flavoring substances used in Europe].

Langman L.J., Kapur B.M. (2006). Toxicology: then and now. *Clinical Biochemistry* **39,** 498–510. [This paper is review the historical progress of clinical and forensic toxicology by exploring analytical techniques in drug analysis, differing biological matrices, clinical toxicology, therapeutic drug management, workplace drug testing, and pharmacodynamic monitoring and pharmacogenetics].

Lathers C.M. (2001). Role of veterinary medicine in public health: antibiotic use in food animals and humans and the effect on evolution of antibacterial resistance. *Journal of Clinical Pharmacology* **41**, 595-599. [This paper describes that there are many ways in which veterinary medicine plays a very important role in public health].

Linton A:H., Howe K., Richmond M.H., Clements H.M., Osborne A.D. Handley B. (1978). Attempts to Displace the Indigenous Antibiotic Resistant Gut Flora of Chicken by Feeding Sensitive Strains of *Escherichia coli* Prior to Slaughter. *Journal of Applied Microbiology* **45**, 239–247. [Attempts to limit the use of antibiotics have not, in general, resulted in the gut flora in farm animals becoming predominantly sensitive. Partial success has been demonstrated, however, by feeding chickens with antibiotic sensitive *Escherichia coli* known to be good colonizers of the chicken gut. Where feeding was done prior to slaughter a corresponding reduction in carcass contamination by resistant *E. coli* was observed].

Madden J.P., Goodman S.J., Guthrie H.A. (1976). Validity of the 24-hr recall. *Journal of the American Dietetic Association* **68,** 143–147. [Tests of the validity of the 24-hr. dietary recall were done by comparing actual with recalled intakes for eight nutrients and the MAR (mean adequacy ratio) for a sample of seventy-six subjects age sixty years or older].

McEvoy J.D.G. (2002). Contamination of animal feedstuffs as a cause of residues in food: a review of regulatory aspects, incidence and control. *Analytica Chimica Acta* **473**, 3-26. [This paper reviews the legislative framework controlling the use of veterinary medicines and zootechnical food additives in the EU. From a contamination perspective, 'problem' compounds include sulphonamides, tetracyclines, nitroimidazoles, nitrofurans, ionophore coccidiostats and nicarbazin. The literature on each of these is reviewed and examples of interventions to minimize contamination are given].

Milagro R., Toldrá F. (2008). Veterinary drug residues in meat: Concerns and rapid methods for detection. *Meat Science* **78**, 60-67. [Different rapid methods having easy performance, high sensitivity and high throughput have been proposed and are being extensively used. These methods as well as other new methods are reviewed in this manuscript].

Mourot D., Loussourorn S. (1981). Sensibilite´ des ferments lactiques aux antibiotics utilise´s enme´decine ve´te´rinaire. *Revue de Médecine Vétérinaire* **157**, 175–177. [Should they be introduced throughout the life of the animal along the enrichment of food fatty acids n-3 or on a shorter period before the slaughter? This question is the subject of this study].

Ngowi A.V., Mbise T.J., Ijani, A.S., London L., Ajayi O.C. (2007). Pesticides use by smallholder farmers in vegetable production in Northern Tanzania. *Crop Protection* **26**, 1617–1624. [Based on the use of questionnaires and interviews that were conducted in Arumeru, Monduli, Karatu, and Moshi rural districts, this study investigates farmers' practices on vegetable pest management using pesticides and related cost and health effects. The types of pesticides used by the farmers in the study areas were insecticides (59%), fungicides (29%) and herbicides (10%) with the remaining 2% being rodenticides].

NRC (1983). Risk Assessment in the Federal Government: Managing the Process, National Research Council. 38 National Academy of Sciences Press, Washington DC, USA. [This report explores the intricate relations between science and policy in a field - the assessment of the risk of cancer and other adverse health effects associated with exposure of humans to toxic substances].

Parmar B., Miller P.F., Burt R. (1997). Stepwise approaches for estimating the intakes of chemicals in food. *Regulatory Toxicology and Pharmacology* **26**, 44-51. [This paper reviews the nature and relevance of the factors affecting the collection of these two data sets and the procedures available for combining them to estimate consumer exposure. Considerable expertise and judgment are necessary to obtain an estimate of exposure that is robust enough for risk management purposes].

Pennycook F.R., Diamand E.M., Watterson A., Howard V. (2004). Modeling the dietary pesticide exposures of young children. *International Journal of Occupational and Environmental Health* **10,** 304-309. [In this work a stepped approach was used to assess the exposures of $1^{1/2}$–$4^{1/2}$-year-old children in the United Kingdom to residues of pesticides (dithiocarbamates; phosmet; carbendazim) found in apples and pears. The actual risk was quantified by stochastically modeling consumption, from dietary survey data, with individual body weights].

Petersen B.J., Chaisson C.F., Douglass J.S. (1994). Use of food-intake surveys to estimate exposures to nonnutrients. *American Journal of Clinical Nutrition*, **59**(Suppl.), 240-243. [This paper describes several steps which must be taken in estimating inteke of dietary nonnutrients].

Petersen B.J. (2000). Probabilistic modeling: theory and practice. Food *Additives and Contaminants* 1**7**(7), 591-599. [The practical application of Monte Carlo to risk assessments is presented along with an evaluation of the input parameters. Topics also discussed include considerations of the requirements for precision and procedures for validation of assessments].

Rees N.M.A., Tennant D.R. (1993). Estimating consumer intakes of food chemical contaminants. In D. H. Watson (Ed.), Safety of chemicals in food: Chemical contaminants 175-181. Chichester: Ellis Horwood. [This work describes four basic guiding principles which must be followed when estimating chemical exposure].

Renwick A.G., Barlow S., Hertz-Picciotto I., Boobis A.R., Dybing E., Edler L., Eisenbrand G., Grieg J.B., Kleiner J., Lambe J., Muller D.J.G., Smith M.R., Tritscher A., Tuijelaars S., van den Brandt P.A., Walker R., Kroes R., (2003). Risk characterisation of chemicals in food and diet. *Food and Chemical Toxicology* **41**, 1211–1271. [This report presents a review of risk characterisation, the final step in risk assessment of exposures to food chemicals.].

Roberts M.C. (1996). Tetracycline resistance determinants: mechanisms of action, regulation of expression, genetic mobility, and distribution. *FEMS Microbiological Reviews* **19**, 1–24. [This paper describes tetracycline resistance determinants: mechanisms of action, regulation of expression, genetic mobility, and distribution].

Rooklidge S.J. (2004). Environmental antimicrobial contamination from terraccumulation and diffuse pollution pathways. *Science of the Total Environment* **35**,1–13. [This review critically examines recent global trends of bacterial resistance, antimicrobial contaminant pathways from agriculture and water treatment processes, and the need to incorporate diffuse pathways into risk assessment and treatment system design].

Rutalj M., Bažulić D., Sapunar-Postružnik J., Živković J., Ljubičić I. (1996). Determination of Quinoxaline-2-carboxilyc Acid (QCA) in Swine Liver and Muscle: *Food Additives and Contaminants*. **13**, 879-882. [In this work the concentration of quinoxaline-2-carboxylic acid (QCA) determined by HPLC after alkaline hydrolysis of liver and muscle of swine. After the 77th day of therapy QCA was found in samples of liver (9.7 ng/g)].

Saieva C., Aprea C., Tumino R., Masala G., Salvini S., Frasca G., et al. (2004). Twenty-four-hour urinary excretion of ten pesticide metabolites in healthy adults in two different areas of Italy (Florence and Ragusa). *Science of Total Environment* **332**, 71–80. [In this study are measured the 24-h urinary excretion of 10 pesticide metabolites to evaluate non-occupational exposure to pesticides in the general population in two different areas in Italy. They were collected 24-h urine samples from 69 healthy adults residing in Florence (Central Italy, *n*=51) and Ragusa (Southern Italy, *n*=18)].

Sammartino M.P., Bellanti F., Castrucci M., Ruiu D., Visco G., Zoccarato T. (2008). Ecopharmacology: Deliberated or casual dispersion of pharmaceutical principles, phytosanitary, personal health care and veterinary products in environment needs a multivariate analysis or expert systems for the control, the measure and the remediation. *Microchemical Journal* **88**, 201–209. [This is review about Ecopharmacology: Deliberated or casual dispersion of pharmaceutical principles, phytosanitary, personal health care and veterinary products in environment needs a multivariate analysis or expert systems for the control, the measure and the remediation].

SANCO/10684/2009, 2010. Method Validation and Quality Control Procedures for Pesticide Residues Analysis in Food and Feed. European Commission, Director- ate General Health and Consumer Protection, 1 January. [The document describes the method validation and analytical quality control (AQC) requirements to support the validity of data used for checking compliance with maximum residue limits (MRLs), enforcement actions, or assessment of consumer exposure to pesticides].

Schwarz S., Chaslus-Dancla E. (2001). Use of antimicrobials in veterinary medicine and mechanisms of resistance. *Veterinary Research* **32**, 201-225. [This review deals with the application of antimicrobial agents in veterinary medicine and food animal production and the possible consequences arising from the widespread and multipurpose use of antimicrobials. The various mechanisms that bacteria have developed to escape the inhibitory effects of the antimicrobials most frequently used in the veterinary field are reported in detail].

Sengeløv G., Angersø Y., Halling-Sørensen B., Badola S.B., Andersen J.S., Jensen L.B. (2003). Bacterial antibiotic resistance levels in Danish farmland as a result of treatment with pig manure slurry. *Environment International* **28**, 587–595.[In this paper resistance to tetracycline, macrolides and streptomycin was measured for a period of 8 months in soil bacteria obtained from farmland treated with pig manure slurry. This was done by spread plating bacteria on selective media (Luria Bertani (LB) medium supplemented with antibiotics). To account for seasonal variations in numbers of soil bacteria, ratios of resistant bacteria divided by total count on nonselective plates were calculated].

Séveno N.A., Kallifidas D., Smalla K., van Elsas J.D., Collard J.M., Karagouni A.D., Wellington E.M.H. (2002). Occurrence and reservoirs of antibiotic resistance genes in the environment. *Reviews in Medical Microbiology* **13**, 15-27. [This paper is review about occurrence and reservoirs of antibiotic resistance genes in the environment].

Slob W. (2006). Probabilistic dietary exposure assessment taking into account variability in both the amount and frequency of consumption. *Food and Chemical Toxicology* **44**, 933-951. [Probabilistic dietary exposure assessments that are fully based on Monte Carlo sampling from raw intake data may not be appropriate. This paper shows that the data should first be analyzed by using a statistical model that is able to take the various dimensions o food consumption patterns into account].

SSC (2000). First Report on the Harmonisation of Risk Assessment Procedures – The Report of the Scientific Steering Committee’s Working Group on Harmonisation of Risk Assessment Procedures in the Scientific Committees Advising the European Commission in the Area of Human and Environmental Health. Scientific Steering Committee, EU, Brussels. (http://ec.europa.eu.int/comm/food/fs/sc/ssc/out83_en.pdf) [The principal purpose of this Report is to promote an active debate on current practices for risk assessment used by the Scientific Committees of DG SANCO and to make proposals for developing convergent approaches which will aid harmonisation. Progressive harmonisation of human health and environmental protection risk assessment procedures within the EU is both of practical importance and scientifically sound].

SSC (2003). The Future of Risk Assessment in the European Union. Second report on the Harmonisation of Risk Assessment Procedures. Scientific Steering Committee, EU, Brussels. (http://ec.europa.eu/food/fs/sc/ssc/out361_en.pdf). [The intention of this work is to identify aspects where a more harmonised approach would be beneficial and where appropriate to make recommendations as to how this might be achieved. In the main report summaries are provided of the key issues and proposals as to how progress can be made in many aspects more detailed information is provided in the appendices].

Teuber M. (2001). Veterinary use and antibiotic resistance. *Current Opinion in Microbiology* **4**, 493–499. [Globally, an estimated 50% of all antimicrobials serve veterinary purposes. Bacteria that inevitably develop antibiotic resistance in animals comprise food-borne pathogens, opportunistic pathogens and commensal bacteria. The same antibiotic resistance genes and gene transfer mechanisms can be found in the microfloras of animals and humans. Direct contact, food and water link animal and human habitats. The accumulation of resistant bacteria by the use of antibiotics in agriculture and veterinary medicine and the spread of such bacteria via agriculture and direct contamination are documented].

USDA (2008). Pesticide Data Program: annual summary, calendar year 2007. Washington, DC, United States Department of Agriculture, Agricultural Marketing Service (http://www.ams.usda.gov/science/pdp/Summary2007.pdf) [The U.S. Department of Agriculture (USDA) Agricultural Marketing Service (AMS) was charged with designing and implementing the Pesticide Data Program (PDP) to collect data on pesticide residues in food. This summary presents results for samples collected in 2007].

USEPA (1996). Residue chemistry test guidelines. OPPTS 860.1520. Processed food/feed. Washington, DC, United States Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances (EPA 712-C-96-184 (http://fedbbs.access.gpo.gov/library/epa_860/860-1520.pdf) [This guideline is intended to meet testing requirements of both the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136, *et seq.*) and the Federal Food,

Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 301, *et seq.*)].

USEPA (1998). Guidance for submission of probabilistic human health exposure assessments to the Office of Pesticide Programs. Washington, DC, United States Environmental Protection Agency, Office of Pesticide Programs (http://www.epa.gov/fedrgstr/EPA-PEST/1998/November/Day-05/6021.pdf). [This science policy document was developed to establish guidance for submission and review of probabilistic human health exposure assessments to the Agency's Office of Pesticide Programs].

USEPA (2000a). Guidance for refining anticipated residue estimates for use in acute dietary probabilistic risk assessment. Washington, DC, United States Environmental Protection Agency, Office of Pesticide Programs (http://www.epa.gov/pesticides/trac/science/residues.pdf). [This document provides guidance to registrants, other test sponsors and interested parties, and data reviewers on the extent and quality of pesticide residue and ancillary data needed to support the use of more refined “anticipated residues” in acute dietary probabilistic exposure assessments].

USEPA (2000b). Assigning values to non-detected/non-quantified pesticide residues in human health food exposure assessments. Washington, DC, United States Environmental Protection Agency, Office of Pesticide Programs (http://www.epa.gov/fedrgstr/EPA-PEST/2000/March/Day-31/6047.pdf) [This document was drafted for the purpose of providing non-binding guidance to interested stakeholders regarding the evaluation of non-detects in pesticide risk assessments].

USEPA (2001). General principles for performing aggregate exposure and risk assessments. Washington, DC, United States Environmental Protection Agency, Office of Pesticide Programs (http://www.epa.gov/pesticides/trac/science/aggregate.pdf). [This document is organized to present an overview of aggregate exposure and risk assessment highlighting revised and expanded concepts].

USEPA (2002). Guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity. Washington, DC, United States Environmental Protection Agency, Office of Pesticide Programs (http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf). [The purpose of this guidance is to set forth the basic assumptions, principles, and analytical framework that are recommended for use by OPP risk assessors in conducting cumulative risk assessments. It is also intended to inform decision makers and the public of the principles and procedures generally followed in the conduct of cumulative risk assessments on pesticide chemicals].

USFDA (2004a). Total diet study. Washington, DC, United States Food and Drug Administration, Center for Food Safety and Applied Nutrition (http://www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/TotalDietStudy/default.htm). [The Total Diet Study (TDS), sometimes called the market basket study, is an ongoing FDA program that determines levels of various contaminants and nutrients in foods].

USFDA (2004b). Pesticide Program residue monitoring 2002. Rockville, MD, USA, United States Department of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition (http://vm.cfsan.fda.gov/~dms/pes02rep.html). [This document is the sixteenth annual report summarizing the results of the Food and Drug Administration's (FDA) pesticide residue monitoring program. This report includes findings obtained during FY 2002 (October 1, 2001 through September 30, 2002) under regulatory and incidence/level monitoring. Selected Total Diet Study findings for 2002 are also presented].

Vragović N., Bažulić D., Njari B. (2011). Risk assessment of streptomycin and tetracycline residues in meat and milk on Croatian market. *Food and Chemical Toxicolog*, ***49***, 352-355. [This paper presents quantitative risk assessment of streptomycin and tetracycline based on acceptable daily intake, daily consumption of milk and meat in Croatia and residues of these two veterinary drugs in this type of food].

WHO (1985). Guidelines for the study of dietary intakes of chemical contaminants. Geneva, Switzerland, World Health Organization (WHO Offset Publication No. 87). [These Guidelines are designed to assist countries in initiating studies of the dietary intake of contaminants at the national level by providing detailed procedures and methods by which such studies may be conducted].

WHO (1992). Assessment of dietary intake of chemical contaminants. Geneva, Switzerland, World Health Organization, Global Environment Monitoring System Food Contamination Monitoring and Assessment Programme (WHO/HPP/FOS/92.6). [Total diet studies are designed to assess chronic dietary exposure to food chemicals actually ingested by the population living in a country and, if possible, population subgroups].

WHO (1995) WHO/FNU/FOS/95.3 , Application of risk analysis to food standards issues, Report of the Joint FAO/WHO Expert Consultation, Geneva, Switzerland 13 - 17 March 1995. [The main objective of the Consultation was to provide recommendations to FAO, WHO, CAC and the member countries concerning the most appropriate approach to the application of risk analysis to food standards and safety issues].

WHO (2002a). – WHO global strategy for food safety: safer food for better health. WHO, Geneva. [This work describes approaches how to reduce the health and social burden of foodborne disease].

WHO (2002b). GEMS/Food Total Diet Studies. Report of the 2nd international workshop on total diet studies, Brisbane, 4–15 February 2002. Geneva. [The workshop consist of presentations by experts on total diet studies that had been conducted in different countries].

WHO (2008). Guidelines for drinking-water quality, 3rd ed. incorporating 1st and 2nd addenda. Vol. 1. Recommendations. Geneva, World Health Organization. (http://www.who.int/water_sanitation_health/dwq/gdwq3rev/en/index.html) [The Guidelines describes a "Framework for Drinking-water Safety" and discusses the roles and responsibilities of different stakeholders, including the complementary roles of national regulators, suppliers, communities and independent "surveillance" agencies].

Witte W. (2000). Selective pressure by antibiotic use in livestock. *International Journal of Antimicrobial Agents* **16**, 19–24. [Selective pressure exerted by the use of antibiotics as growth promoters in food animals appears to have created large reservoirs of transferable antibiotic resistance in these ecosystems. This first became evident for oxytetracycline and later for the streptothricin antibiotic nurseothricin, for which a transfer of relevant resistance determinants (*sat* genes) to bacterial pathogens of humans was demonstrated].

WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) (http://www.wto.org/English/tratop_e/sps_e/spsagr_e.htm). [This Agreement applies to all sanitary and phytosanitary measures which may, directly or indirectly, affect international trade. Such measures shall be developed and applied in accordance with the provisions of this Agreement].

Biographical Sketch

Natalija Vragović, received her Degree and Ph.D in Veterinary Medicine (Veterinary Public Health and Food Safety) at the University of Zagreb (Croatia) in 2006 and 2010, respectively.
Since 2006 she is in the research staff at the Department of Residues Analysis of the Center for Food Control, Croatia where she developed her expertise on risk assessment of veterinary drug residues in food of animal origin.
Research interests: food safety, risk assessment, dietary exposure, chemicals in food, residues analysis.
Author of about 20 research papers in international journals and numerous presentations in international scientific meetings on food safety.