Reactive oxygen and nitrogen species (ROS/RNS) are essential for energy supply, chemical signalling, detoxification, and immune function and, as a consequence, continuously produced in the human body. For the most part they are exquisitely controlled but over-production, exposure to external oxidants or the failure of antioxidant defence mechanisms are implicated in damage to DNA, lipids and proteins. Damage to these biomolecules is associated with increased risk of chronic diseases normally associated with ageing including cancer and cardiovascular disease.

The Antioxidant Hypothesis suggests that reducing agents prevent oxidative damage and thus increased levels will also reduce the risk of chronic disease. This lead to the suggestion that increased intake of dietary compounds, some of which are capable of acting as chemical antioxidants, would be of benefit by augmenting cellular defences and protect components of the cell against oxidative damage and, ultimately, disease. There is compelling epidemiological evidence linking consumption of diets rich in antioxidants, direct and indirect, with reduced risk of developing degenerative disease. However, the enormous focus on this field of research worldwide has generated data that both support and challenge the hypothesis.

Observational studies in humans have demonstrated high intakes of foods rich in dietary antioxidants (i.e. fruit and vegetable, cereals and grains, and some specific oils and fats) and high plasma concentrations of these dietary antioxidants are associated with reduced morbidity and mortality. However, plasma antioxidant concentrations are a measure of intake, rather than a measure of concentration at target sites, and an association is not necessarily causal. Human intervention studies have shown no consistent benefit of increased intake of dietary antioxidants, either individually or in combination as isolates or foods, in the prevention of human diseases. Many arguments have been put forward to explain why these studies have failed to demonstrate an effect consistent with the epidemiology, but few have addressed the underlying and fundamental problems associated with complex nutritional trials.

EUROFEDA was set up under the European Union’s Fifth Framework RTD programme Key Action 1 - Food, Nutrition and Health. It has brought together many of the leading European scientists working in the antioxidant field, from both academia and industry, with the dual aims of critically reviewing existing knowledge and identifying the research necessary to further understanding of the functional effects of dietary antioxidants. Three Task Groups were set up focussing on the areas where research has been most active in the recent past and, it was anticipated, would be critical to future progress; Bioavailability, Biomarkers, and ROS, Gene Expression and Mitochondrial Function. The project gave particular attention to nutritional concerns rather than focusing on effects that are more relevant to the potential use of antioxidants or plant phytochemicals as nutraceuticals.

Conclusions

There is no evidence to support the view that any one dietary antioxidant is more essential than another. Indeed, the protective effects of higher consumption of fruit and vegetables etc. is likely to be explained by a number of different classes of dietary substances contributing to the overall benefit. There is substantial and undisputed proof that diet can prevent or delay the development of many chronic age-related diseases and increased consumption of foods containing a range of the recommended compounds would without doubt confer health benefits for individuals as well as the European population at large.

In general, specific dietary compounds will not make diseased cells or tissues healthy again although there is increasing evidence that some may have a therapeutic role in the treatment of particular diseases (e.g. lycopene and prostate cancer). Increased intake of active compounds will not prevent complex multi-factorial diseases but they may slow their development or inhibit their progression. Whether these compounds should be consumed as complex foods within the habitual diet or as individual or mixed supplements, and the appropriate doses that confer health benefits without additional risk, have yet to be determined. Many scientists remain cautious because of the complexity of human intervention trials and their associated costs, the selection of appropriate test and control groups, the source and dose of the compound of interest and the biological relevance of (bio)markers as well as a lack of validated analytical methods to measure the effect of increased intake. All these issues have played a part in the failure of intervention studies to give consistent data.

The EU is among the world’s leading producers of food and drinks. The industry is worth in excess of 650 billion Euros and it employs over three million people. However, whilst the success of new food products is measured in months, studies validating functional claims are time-consuming and expensive. If Europe is to promote health through diet, products that cater to consumers’ health needs as well as psychological desires need to be developed and proven, scientifically, to be effective. To do this, markers that take into account the development and progression of specific diseases, which also measure benefit and risk for long-term health, must be established. This will mean improvements to existing biomarkers, with respect to selectivity and sensitivity, but also the development of new non-invasive methods.

For individuals as well as groups, such as the elderly or those with specific problems or disease, the influence of genotype, both in terms of benefit and risk, will only increase in importance. However, much more information about foods is also needed including the chemical composition and the concentration, form and location of dietary antioxidants and other important compounds (e.g. glucosinolates). It will be essential to determine whether dietary compounds act via simple chemical reactions or complex signalling pathways since this has implication for risk as well as benefit. We need to know how food processing and preparation influence the release and uptake of active compounds from the food matrix as well as biochemical, physiological and physicochemical factors likely to affect their uptake. Initially, it may be necessary to study the effect of individual dietary compounds, over the short-term, but future work must examine mixtures of different dietary compounds and complex foodstuffs over a longer duration.

EUROFEDA has identified areas crucial for future research in bioavailability, biomarkers, gene expression and mitochondrial function. The nature of the challenges facing nutritional research is such that there will need to be a major investment of resource in multi-disciplinary, collaborative research efforts. Whether this can be achieved, like many of the other questions posed, has yet to be demonstrated. However, without consolidated information, the food industry will not be able to make claims that can be substantiated and consumers will not be given the opportunity to make dietary choices based on scientific evidence.

Introduction

To determine the mechanisms of action through which antioxidant micro-constituents in food prevent disease, an understanding of the factors that constrain their release from the foods, the extent of their absorption, and their ultimate fate is crucial. These issues are often described under the ‘banner’ of bioavailability; a term borrowed from the field of pharmacology, but largely redefined as that fraction of an oral dose (parent compound or active metabolite) from a particular preparation that reaches the systemic circulation.

With the advent of present-day analytical techniques and instrumentation, it is possible to describe the complex chemical nature of our foods with ever increasing degrees of accuracy. However, the types and quantities of the different components in foods have very little bearing on health since only a proportion are absorbed and utilised. Understanding the concept of bioavailability is essential to all involved in food production, nutritional assessment and determining diet-health relationships.

Chapter Two of the review discusses (i) availability for absorption, or ‘bioaccessibility’; (ii) absorption; (iii) tissue distribution; and (iv) bioactivity for vitamins C and E, the carotenoids, plant polyphenols, glucosinolates, selenium and the precursors of glutathione.

Conclusions

- Biokinetic studies are required to improve knowledge about the fate of antioxidant compounds in the body. These will also help to identify the best sources within the diet as well as factors that influence bioavailability. This information is needed in order to interpret and design studies that will determine the range of doses over which beneficial effects of antioxidants occur and allow benefit-risk analyses based on exposure to a specific compound.
- It is important to reveal the relationship between intake of antioxidants and their dose-dependent functional effects in target tissues. Functional effects may be determined as disease endpoints or biomarkers that have been validated with respect to the pathology of a specific disease.
- If the level of an active compound at the target site cannot be measured in humans, the relationship between blood concentrations and levels at target sites should be determined in suitable animal models.
- Benefit-risk analyses should be applied equally to parent molecules and metabolites since the latter may be more or less active, or exhibit other biological effects.

The final goal of all these studies should be to identify optimal intake levels from food based on an evaluation of overall benefit without additional risk.

Future Research

- Studies on how food processing or preparation influences the release and uptake of dietary antioxidants from the food matrix.
- The biochemical, physiological and physicochemical parameters that affect bioavailability.

Research on these topics will be of particular interest to the food industry since the development of functional foods requires knowledge of how dietary sources can be modified to improve the availability and delivery of beneficial compounds.

- Development of existing and new databases describing the antioxidants content of dietary products. This information is essential for future nutritional trials. A major analytical effort will be necessary.
- Exploration and development of suitable animal models, which can be used to determine the relationship between surrogate and target sources (e.g. blood and tissue). Such research is needed because of the limitations imposed on sampling in humans. Alongside studies using animal models the selectivity and sensitivity of current methods should be improved and new non-invasive methods developed for application in human studies.
- Studies should be undertaken to determine the metabolism and degradation of dietary compounds in humans using appropriate animal models and advanced analytical technology and modern methods. This work should include structural elucidation and changes in stereochemistry.
Biomarkers

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Introduction

The term ‘biomarker’ has been adapted from molecular epidemiology to quantitatively or qualitatively describe a change in a biological molecule that has arisen from attack by reactive oxygen, nitrogen or halide species. It is applied equally to products derived from lipids, DNA, proteins and to antioxidant consumption, where the chemical nature of the reaction may be proton abstraction, electron transfer or direct addition. Information regarding the nature of the denaturing radical, as well as the localisation of oxidative stress, may be gleaned from the analysis of discrete biomarkers isolated from tissues/ organelles/ fluids. Biomarkers have, therefore, been used to evaluate the efficacy of many antioxidants in vitro, ex vivo and in vivo but with mixed results, which may reflect too great an expectation on the information biomarkers can yield.

Biomarkers may yield information at three progressive levels: (i) as measurable endpoints of damage to proteins/ amino acids, lipids, and DNA, (ii) as functional markers (e.g. blood flow, platelet aggregation, or cognitive function), and (iii) as endpoints related to specific disease (e.g. lens opacity).

While the clinical symptoms of a disease are endpoints in themselves, in many cases, they are not suitable for early detection of the disease process and, therefore, prevention. A series of biomarkers would be preferred, each validated in sequence and the association between the biomarker and the disease process clearly defined. There is no known biomarker that bridges the gap between exposure and a given endpoint, but increasing knowledge of the functional consequences of damage to biomolecules is bringing this possibility ever closer. Eventually, biomarkers may be proven to relate directly to functional changes and ultimately disease. In the meantime, however, they can yield important information on the nature of radical damage and antioxidant action in vivo, particularly regarding the nature of pro-oxidant effects, compartmentalisation and bioavailability.

A valid biomarker should be a major product of oxidative modification that may be implicated directly in development of disease. The product must be stable, not susceptible to artefactual induction or loss during storage and representative of the balance between oxidative damage generation and clearance (i.e. the steady state, but also possibly applicable to the measurement of cumulative oxidative damage). A biomarker should be free from confounding factors including dietary intake and easily obtained from a valid surrogate tissue or an accessible target tissue; the relationship between the two having been established in advance. The assay used to measure the biomarker should be specific, sensitive, reproducible and robust, and the results within an appropriate range, based on the limits of detection. In addition, normal ranges should be established for each assay, reflecting the age and sex of the subject group. Physiological changes, such as oxidation occurring during exercise, can then be defined in relation to the normal range.

Chapter Three of the review considers the current status of biomarkers for measuring oxidative damage in DNA, lipids and proteins within the context of (in priority order): (i) identity, (ii) linearity, (iii) accuracy, (iii) selectivity, (iv) reproducibility and (v) an appropriate limit of detection (LOD). Commonly used analytical procedures and their limitations are reviewed as well biomarker formation and validity.

Conclusions

- Out of 80 studies reviewed, less than 50% used appropriately validated methodology but 66% of the valid studies showed evidence of benefit.
- Benefit was more frequently observed in populations under oxidative stress at baseline.

Recommendations

- Several validated and biologically relevant markers should be used in a single study.
- Trial design and study power are crucial to success; the parallel group crossover design is the most robust approach where the relative or absolute changes between groups are compared.
- Effects should be evaluated in a dose-dependent manner, which will permit concomitant benefit-risk analyses.
- The subject groups must be well (i.e. not ill) during a study.
- An appropriate biomarker for healthy individuals may not be suitable for individuals with a particular disease. Suitability of a biomarker should be determined separately for healthy individuals and those with clinical symptoms of a specific disease. It should also be remembered that the biomarker may not be appropriate at all stages of the disease and may be disease-specific.

DNA

- 8-oxo-7,8-dihydroguanine (8-oxoGua) is a useful biomarker
- Analysis of resistance to DNA stand breaks alone is inappropriate
- Further work is required on the analysis of oxidised bases other than 8-oxo-7,8-dihydroguanine, enzyme-sensitive sites (in the Comet Assay), etheno- sites and the nucleoside (8-oxo-dGuo) in urine by chromatography or ELISA

Lipids

- Lipid peroxides and isoprostanes are useful biomarkers
- TBARS, MDA, conjugated dienes and lipofuscin are not useful for analysis of human samples (in vivo/ ex vivo)
- Further work is needed with respect to analysis of urinary isoprostanes and breath hydrocarbon gases

Oxidant: Antioxidant ratio

- GSH:GSSG can be usefully applied, provided appropriate precautions are taken in specimen collection, storage and analysis
- Total antioxidant capacity analysis is not useful in determining effects of supplementation with dietary compounds
- Further work is needed to determine whether peroxide measurement will be useful

Proteins

- There are many potentially suitable biomarkers for protein oxidation including nitrated amino acids, protein bound tyrosine oxidation products, protein bound tryptophan products, and methionine sulfoxide. However, at present, these are in the earlier stages of development and validation.
- Thiol and hydroperoxide determination are not appropriate biomarkers
Future Research Needs

- Validation studies should be established for all favoured biomarkers.
- Typical mean values and ranges for all biomarkers in healthy volunteers and patients should be established. These may change as individuals’ age or different diseases progress.
- The kinetics of oxidative biomarker formation and their respective half-lives should be re-examined in view of the kinetics of bioavailability. The influence of genetic polymorphisms on biomarker kinetics should be considered.
- Mutations and sites of oxidative DNA damage should be identified and the role of dietary components in their modulation established.
- The capacity of dietary compounds to protect protein function through prevention of critical amino acid oxidation should be examined.
- Quantitative expression analysis and proteomics should be used to identify the most sensitive biomarkers. These can be used subsequently to discover whether dietary compounds act as simple antioxidants and/or via complex interaction with ROS and cellular signalling pathways.
- Analysis of plasma samples from prospective studies of disease outcome, using validated biomarkers, would establish the relationship between biochemical endpoint and disease development. Ultimately, the relationship between primary biomarkers and disease endpoints should also be determined.

Recommendations for appropriate biomarkers

<table>
<thead>
<tr>
<th>Specific</th>
<th>Stable</th>
<th>Validity</th>
<th>Disease</th>
<th>Dose response</th>
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<tr>
<td>DNA biomarkers</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>8-oxoGua (DNA)</td>
<td>++</td>
<td>? possible artefactual oxidation</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Other oxidised bases</td>
<td>++</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Urinary 8-oxo-dGuo</td>
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<td>++</td>
<td>++</td>
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<td>?</td>
<td>?</td>
<td>++</td>
</tr>
<tr>
<td>Etheno adducts</td>
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<td>++</td>
<td>?</td>
<td>++</td>
</tr>
<tr>
<td>Strand breaks</td>
<td>-</td>
<td>? half-life = few minutes</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Enzyme sites</td>
<td>?</td>
<td>++</td>
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<td>++</td>
</tr>
<tr>
<td>Lipid oxidation biomarkers</td>
<td></td>
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<tr>
<td>TBARS</td>
<td>-</td>
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<td>+/-</td>
<td>-</td>
<td>?</td>
<td>++</td>
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<td>Ethane, pentane</td>
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<td>++</td>
<td>?</td>
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<tr>
<td>Lipofuscin</td>
<td>-</td>
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<td>++</td>
</tr>
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<td>++</td>
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<td>?</td>
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<tr>
<td>Diene conjugates</td>
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<td>-</td>
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<td></td>
</tr>
<tr>
<td>TEAC</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>ORAC</td>
<td>++</td>
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<td>?</td>
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<td>FRAP</td>
<td>-</td>
<td>++</td>
<td>?</td>
<td>++</td>
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<tr>
<td>Resistance to strand breaks</td>
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<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>LDL lag time</td>
<td>-</td>
<td>?</td>
<td>-</td>
<td>++</td>
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<td>-</td>
<td>++</td>
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<td>Protein oxidation biomarkers</td>
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<td>carbonyls</td>
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<td>thiols</td>
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<td>Nitrated amino acid</td>
<td>++</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Protein -Tyr oxidation products</td>
<td>++</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Protein -Trp oxidation products</td>
<td>++</td>
<td>++</td>
<td>?</td>
<td>++</td>
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<tr>
<td>Methylone sulphoxide</td>
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<td>++</td>
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</tr>
<tr>
<td>Hydroxides/ hydroperoxides</td>
<td>++</td>
<td>-</td>
<td>?</td>
<td>++</td>
</tr>
<tr>
<td>Protein 2-adipic semi aldehyde</td>
<td>?</td>
<td>++</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Neoepitopes</td>
<td>?</td>
<td>++</td>
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</tr>
</tbody>
</table>

Key

Specific > Stable > Validity > Disease > Dose response
++ Criterion met with confidence
+ Criterion met
? Criterion not previously fully evaluated
- Criterion not met
**Antioxidants, Reactive Oxygen and Nitrogen Species, Gene Induction and Mitochondrial Function**

Malcolm J. Jackson (Task Group Co-ordinator), Sergio Papa (deputy), Juan Bolaros, Richard Bruckdorfer, Harald Carlsen, Ruan M. Elliott, Jacoba Flier, Helen R. Griffiths, Simon Heales, Birgit Holst, Michele Lorusso, Elizabeth Lund, Jan Ovívind Moskaug, Ulrich Moser, Marco Di Paola, M. Cristina Polidori, Anna Signorile, Wilhelm Stahl, José Viña-Ribes, Siân B. Astley

**Introduction**

In recent years, there has been increasing interest in the possibility that reactive oxygen/nitrogen species (ROS/RNS) may act as signals, or mediators of changes, in cell function, proliferation and differentiation as well as their acknowledged part in cell damage and death. This clearly has implications for understanding the roles and requirements for the antioxidant nutrients since by inference they would also modulate these essential cellular processes. Understanding the relative importance of these disparate functions of oxidants and dietary compounds is therefore crucial to evaluation of antioxidants in the chronic disease processes, ageing and cell death.

A better understanding of the requirements for antioxidants would be gained if it were possible to understand the processes by which ROS/RNS alter cellular function or result in cellular damage. An intimate link is becoming apparent between cellular oxidants, antioxidants, cellular redox and the control of signalling pathways, and gene expression. Cellular redox is increasingly recognised as a crucial mediator and influences multiple metabolic, signalling and transcriptional processes that are all essential for normal cellular functioning and survival.

Relatively few studies have examined the effect of antioxidant compounds at nutritionally relevant levels. The approach has been to use antioxidants and/or pharmacological agents with antioxidant properties at high concentrations in traditional cell models. The potential importance of this field is enormous since by implication the diverse group of dietary compounds known as antioxidants may have the capacity to regulate multiple key cellular processes such as cell proliferation and apoptosis. This has important implications for understanding major disorders such as coronary heart diseases and cancer and their prevention.

Chapter Four of the review describes examples of the processes and pathways influenced by ROS and RNS, and/or antioxidants. A specific section deals with oxidants in mitochondria and their effect on these organelles. Finally, because this rapidly developing field is influenced by developments in novel technologies, which allow rapid evaluation of diverse effects of oxidants on gene and protein expression, there is a brief description of these and suggestions where they may play a role in future research.

**Conclusions**

- ROS/RNS act through key signalling and response systems of cells and have an important role in modulating changes in gene expression and cell function.
- Mitochondria are a major source of oxidants and these organelles are highly susceptible to oxidative damage.
- Some oxidant-regulated changes in gene expression are protective (e.g. apoptosis) and it is not clear (i) what effect antioxidants may have on these mechanisms or (ii) whether it is appropriate to attempt to manipulate them.

- Oxidant-regulated changes in gene expression can be modified by a number of reducing agents (i.e. antioxidants) but the relevance of these studies *in vitro* to potential effects of dietary compounds on gene regulation in man is unclear.
- Changes in gene expression may be markers of oxidant stress but the implications of these changes are not understood.
- There is evidence that some dietary substances can modify cellular redox. Further work is required to comprehend the potential effects of diet on redox-related changes in gene expression.
- Much of the data available in this area have been obtained from cell culture and animal experiments. Improved and more sophisticated animal models are needed to help elucidate antioxidant mechanisms of action. These may include conditional knockout and transgenic mice and non-invasive reporter models for imaging gene expression.

**Future Research Needs**

- The relevance of data from studies involving transformed cancer cell lines and non-physiological oxygen tensions requires re-assessment.
- More information is needed on the role and effect of genetic differences on the generation and responses to ROS/RNS.
- It is essential to identify tissue specific patterns of gene expression that are linked with disease states and modified by dietary constituents.
- Studies are required to determine whether DNA arrays can be used for risk:benefit analyses of nutrients and non-nutrients at levels relevant to dietary intakes.
- Development of a redox-regulated gene microarray chip may help to determine the mechanisms of action of dietary compounds as individual compounds and mixtures in the form of complex foods.
- The implications of a reduction in mitochondrial complex activity, unrelated to changes in cellular ATP levels and effects of diet on this, needs to be investigated.

**Cellular oxidants, endogenous antioxidants and gene expression: Known or suggested interactions *in vivo* and potential interactions yet to be considered**

Solid lines = known or suggested interaction *in vivo*  
Broken lines = potential interactions
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6. Departamento de Fisologia, Facultad de Medicina, Universidad de Valencia, SPAIN
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24. Pharmaceutical Sciences, Aston University, Birmingham, UK
25. Rigshospitalet, University Hospital, Copenhagen, DENMARK
26. RIKILT-DLO, Wageningen, THE NETHERLANDS
27. Roche Vitamins Europe Ltd., Basel, SWITZERLAND
28. Rowett Research Institute, Aberdeen, SCOTLAND
29. The L. Rydygier Medical University, Department of Clinical Biochemistry, Bydgoszcz, POLAND
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