Food and Agriculture Organization of the United Nations

World Health Organization

**JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES**
**Ninety-fourth meeting (Residues of veterinary drugs)**
**Virtual meeting, 16–27 May 2022**

# SUMMARY AND CONCLUSIONS

*Issued on 3 June 2022*

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held virtually from16 to 27 May 2022. The purpose of the meeting was to evaluate residues of certain veterinary drugs in food.

Professor (Emeritus) Alan R. Boobis served as Chairperson, and Dr Alan Chicoine served as Vice-Chairperson.

Mr Soren Madsen, World Health Organization (WHO), and Dr Vittorio Fattori, Food and Agriculture Organization of the United Nations (FAO), served as Joint Secretaries.

The present meeting was the ninety-fourth in a series of similar meetings and the twenty-fourth JECFA meeting specifically convened to consider residues of veterinary drugs in food. The tasks before the Committee were to further elaborate principles for evaluating the safety of residues of veterinary drugs in food, establishing acceptable daily intakes (ADIs) and acute reference doses (ARfDs), and recommending maximum residue limits (MRLs) for such residues when the drugs under consideration are administered to food-producing animals in accordance with good practice in the use of veterinary drugs (GVP); to evaluate the safety of residues of certain veterinary drugs; and to respond to specific requests from the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). In total, four veterinary drugs were evaluated by the Committee.

The report of the meeting will be published in the WHO Technical Report Series (No. 1041). Its presentation will be similar to that of previous reports; namely, general considerations, comments on specific substances and recommendations. The report will include an annex (similar to Annex 1 in this summary) summarizing the conclusions reached by the Committee relating to ADIs, dietary exposure and MRLs.

Items of a general nature that contain information that the Committee would like to disseminate quickly are included in Annex 2. Future work and recommendations arising from the meeting are summarized in Annex 3. The participants are listed in Annex 4.

Toxicological monographs summarizing the data that were considered by the Committee in establishing ADIs will be published in WHO Food Additives Series No. 85. Residue monographs summarizing the data that were considered by the Committee in recommending MRLs will be published in FAO JECFA Monograph No. 28.

More information on the work of JECFA is available at:

https://www.fao.org/food-safety/scientific-advice/jecfa/en/

and

https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)/



## Annex 1

### *Recommendations on the substances on the agenda*

**Imidacloprid** (parasiticide)

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| Acceptable daily intake | In view of the absence of a study to assess the impact of imidacloprid on representative human intestinal microbiota, it was not possible to determine an mADI, thus the Committee was unable to establish an ADI for imidacloprid.<br><br>The Committee established a toxicological acceptable daily intake (tADI) of 0–0.05 mg/kg bw on the basis of a NOAEL of 5.25 mg/kg body weight (bw) per day for decreased body weight (bw) gain in the extended one-generation reproduction study, with the application of a safety factor of 100 to allow for interspecies and intraspecies differences. |
| Acute reference dose | In view of the absence of a study to assess the impact of imidacloprid on representative human intestinal microbiota, it was not possible to determine an mARfD, thus the Committee was unable to establish an ARfD for imidacloprid.<br><br>The Committee established a toxicological acute reference dose (tARfD) of 0.09 mg/kg bw based on a $BMD_{05}$ of 9 mg/kg bw reported by Cal EPA for an acute neurotoxicity study in rats and a safety factor of 100 to allow for interspecies and intraspecies differences. This value was supported by a NOAEL of 7.5 mg/kg bw per day for tremors in a 90-day toxicity study in dogs occurring during the first week of treatment, although it is not known whether tremors occurred after the first dose. |

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| Estimated chronic dietary exposure | While estimates of dietary exposure were derived, there are no HBGVs with which to compare them.<br><br>Based on incurred residues in Atlantic salmon (fillet) and a withdrawal period of 98 degree-days:<br>The global estimate of chronic dietary exposure (GECDE) for adults and the elderly is 1.0 µg/kg bw per day.<br>The GECDE for children and adolescents is 2.7 µg/kg bw per day.<br>The GECDE for infants and toddlers is 0.9 µg/kg bw per day.<br><br>Based on incurred residues in fish meat and a withdrawal period of 98 degree-days:<br>The GECDE for adults and the elderly is 1.8 µg/kg bw per day.<br>The GECDE for children and adolescents is 3.8 µg/kg bw per day.<br>The GECDE for infants and toddlers is 1.2 µg/kg bw per day. |
| Estimated acute dietary exposure | Acute dietary exposures were assessed at 98 degree-days post dose. The adjusted (MR:TRR = 0.7) 95/95 UTL concentrations used were 859 µg/kg. No ARfD was available.<br><br>Based on consumption of Atlantic salmon:<br>The GEADE for adults is 6.2 µg/kg bw per day.<br>The GEADE for children is 6.6 µg/kg bw per day.<br><br>Based on consumption of all fin fish:<br>The GEADE for adults is 34.1 µg/kg bw per day.<br>The GEADE for children is 23.8 µg/kg bw per day. |
| Residue definition | The marker residue for imidacloprid in fillets of salmonids is the parent molecule, imidacloprid. |
| Maximum residue limits | As the Committee could not establish an ADI or an ARfD, an MRL could not be recommended for imidacloprid. |

**Ivermectin** (broad-spectrum antiparasitic agent)

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| Acceptable daily intake | The Committee established an ADI of 0–10 µg/kg body weight at the eighty-first meeting. |
| Acute reference dose | The Committee established an ARfD of 200 µg/kg body weight at the eighty-first meeting. |
| Residue definition | The marker residue in sheep, pigs and goats is ivermectin $B_{1a}$ ($H_2B_{1a}$, or *22,23*-dihydroavermectin B1a). |

Estimated chronic dietary exposure

The GECDE for adults and the elderly is 0.72 µg/kg bw per day, which represents 7.2% of the upper bound of the ADI of 10 µg/kg bw.

The GECDE for children and adolescents is 0.93 µg/kg bw per day, which represents 9.3% of the upper bound of the ADI of 10 µg/kg bw.

The GECDE for infants and toddlers is 0.48 µg/kg bw per day, which represents 4.8% of the upper bound of the ADI of 10 µg/kg bw.

Estimated acute dietary exposure

The GEADE for cattle muscle, applicable to children and the general population, is 69 µg/kg bw, which represents 35% of the ARfD of 200 µg/kg bw.

The GEADE for sheep muscle, applicable to children and the general population, is 73 µg/kg bw, which represents 37% of the ARfD of 200 µg/kg bw.

The GEADE for pig muscle, applicable to children and the general population, is 30 µg/kg bw, which represents 15% of the ARfD of 200 µg/kg bw.

***Recommended maximum residue limits (MRLs)***

| Species | Muscle (µg/kg) | Liver (µg/kg) | Kidney (µg/kg) | Fat (µg/kg) |
|---|---|---|---|---|
| Pigs | 15 | 30 | 20 | 50 |
| Sheep and goats | 30 | 60 | 20 | 100 |

**Nicarbazin** (coccidiostat)

Toxicological effects

The NOAEL was 60 mg/kg bw per day (equivalent to 42.5 mg/kg bw per day of DNC) due to prominent liver lobulation, observed in a study of developmental toxicity in the rabbit.

Uncertainty factor

When considering nicarbazin it is DNC that is the toxic component, and its absorption alone or in a mixture with HDP is substantially less (< 5%) than when formed from ingested nicarbazin. As DNC is the residue of concern and there is no nicarbazin in products from treated animals, the Committee concluded that despite limitations in the database, a reduction in the default safety factor of 100 used to account for interspecies and intraspecies variability, would be justified. The Committee was unable to quantify just how much of a reduction would be appropriate, but concluded that 50 could certainly be supported, and would still result in a conservative evaluation.

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| Toxicological ADI | The tADI for nicarbazin was established at 0–0.9 mg/kg bw (DNC). |
| Microbiological effects | Nicarbazin and/or its metabolites show no antimicrobial activity towards representative bacteria of the human intestinal microbiota. |
| Microbiological ADI | The Committee concluded that it was not necessary to establish an mADI for nicarbazin. |
| Acceptable daily intake | The ADI for nicarbazin was established at 0–0.9mg/kg bw based on toxicological effects. |
| Acute reference dose | The Committee concluded that it was not necessary to establish an ARfD for nicarbazin. |
| Residue definition | The marker residue in chickens is DNC. |
| Estimated dietary exposure | Based on incurred DNC residues in chicken muscle, offal, and skin with fat, at 24 hours withdrawal time and 125 mg/kg feed:<br>The global estimate of chronic dietary exposure (GECDE) for adults and the elderly is 120 µg/kg body weight (bw) per day, which represents 13% of the upper bound of the ADI of 900 µg/kg bw.<br>The GECDE for children and adolescents is 160 µg/kg bw per day, which represents 18% of the upper bound of the ADI of 900 µg/kg bw.<br>The GECDE for infants and toddlers is 210 µg/kg bw per day, which represents 23% of the upper bound of the ADI of 900 µg/kg bw.<br><br>Based on incurred DNC residues in chicken muscle, offal, and skin with fat, at zero days withdrawal time and 50 mg/kg feed:<br>The GECDE for adults and the elderly is 95 µg/kg bw per day, which represents 11% of the upper bound of the ADI of 900 µg/kg bw.<br>The GECDE for children and adolescents is 120 µg/kg bw per day, which represents 14% of the upper bound of the ADI of 900 µg/kg bw.<br>The GECDE for infants and toddlers is 160 µg/kg bw per day, which represents 18% of the upper bound of the ADI of 900 µg/kg bw. |

***Recommended maximum residue limits (MRLs)***

| Species | Muscle (µg/kg) | Liver (µg/kg) | Kidney (µg/kg) | Skin with fat (µg/kg) |
|---|---|---|---|---|
| Chicken | 4000 | 15 000 | 8000 | 4000 |

**Selamectin** (broad-spectrum parasiticide)

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| Acceptable daily intake | The Committee withdrew the previous ADI and established an ADI of 0–0.05 mg/kg bw, based on a NOAEL of 5 mg/kg bw per day for increased liver and uterus/cervix weights at 15 mg/kg bw per day in a one-year rat study, with application of a safety factor of 100 to account for interspecies and intraspecies variability. Although the NOAEL for effects seen in a 13-week dietary neurotoxicity/toxicity study in rats, assessed by the Committee at its last meeting was 1 mg/kg bw per day, the LOAEL at 15 mg/kg bw per day, and the effects observed were the same as those on which the ADI is based. The Committee concluded that the ADI established at the present meeting would be sufficiently protective of these findings. |
| Acute reference dose | The Committee concluded that the ARfD of 0.4 mg/kg bw established at the eighty-eighth meeting was still appropriate. |
| Residue definition | The marker residue in Atlantic salmon fillet is selamectin. |
| Estimated dietary exposure | Dietary exposure was assessed for some possible scenarios, but no GVP has been established. |
| Maximum residue limits | Specific MRLs could not be recommended at this time due to a lack of established GVP. |

## Annex 2

## *General considerations*

*An edited version of this section will be included in the report of the ninety-fourth meeting of JECFA. It is reproduced here so that the information can be disseminated quickly.*

### Comments on the parallel review process

As previously noted by the Committee at the eighty-eighth meeting, JECFA remains supportive of the parallel review process. Based on the experience gained through the evaluations of selamectin at the eighty-eighth and ninety-fourth meetings, the Committee concluded that the process and requirements for this parallel review approach should be essentially the same as those for a compound that has already received registration in a Member State. This includes providing all necessary information required to establish a health-based guidance value (HBGV) and recommend maximum residue limits (MRLs) in the tissue(s) of interest, as is the mandate of JECFA. The Committee reiterates that specific MRLs cannot be recommended without established good veterinary practice (GVP) for a product in at least one Member State. A range of preliminary proposed MRL values, which may be useful in informing risk management, were derived for selamectin based on the currently available data.

### Estimation of dietary exposure to veterinary drug residues as performed by JECFA

The current JECFA approach is to derive estimates of acute and chronic dietary exposure for two population groups; the general population and children. In some respects there is a degree of double-counting in this approach, as children are part of the general population.

Under the global estimate of chronic dietary exposure (GECDE) the maximum mean consumption and maximum highest reliable percentile consumption values, across surveys, are used to estimate dietary exposure. Food consumption data are derived from the FAO/WHO chronic individual food consumption database – summary statistics (CIFOCOss). Prior to the eighty-eighth meeting of JECFA, CIFOCOss changed to using the FoodEx 2 food description system and at the time of the eighty-eighth meeting of the Committee food consumption data were only available expressed on a "g/day" basis. On this basis the highest food consumption levels for most foods will be by the adult population.

Since the eighty-eighth meeting of the Committee further work on CIFOCOss has resulted in food consumption data now being available on a "g/day" or a "g/kg body weight per day" basis. The latter presentation of the data has advantages, as no assumption need be made concerning the body weights of different populations. However, for food consumption expressed on this basis, in most cases the highest food consumption values will be for infants and toddlers. This has the potential to result in the GECDE estimates for children and the general population being identical, or very similar.

Food consumption data in CIFOCOss are available for a range of sub-populations. These sub-populations are assigned to one of four age classes; all (general population), adults and the elderly, children and adolescents, and infants and toddlers.

Use of the GECDE has been adopted for evaluations conducted by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) as a measure of high consumer dietary exposure. JMPR routinely estimates mean and GECDE dietary exposure estimates for: all (general population), all adults, adult females, children and adolescents, and infants and toddlers.

While further discussions are required to fully harmonize dietary exposure estimation methods between JECFA veterinary drugs and JMPR, it is proposed that a partial alignment of the sub-populations should be performed as an interim measure.

Recommendations by the Committee concerning the estimation of dietary exposure to veterinary drug residues as performed by JECFA are provided in Annex 3.

**A risk-based decision tree approach for the safety evaluation of residues of veterinary drugs**

JECFA is sometimes asked for advice on veterinary drugs for which the establishment of health-based guidance values (HBGVs) and recommendation of maximum residue limits (MRLs) is not appropriate, for example when they are genotoxic carcinogens. In other situations there may not be a full data package, such as for "old" drugs where there is still a use, drugs with no commercial sponsor, drugs no longer in use but which cause contamination of food due to environmental persistence, or the misuse or abuse of drugs. In the early 2000s, a number of activities were undertaken to discuss possible approaches to these situations, including a Joint FAO/WHO "Technical workshop on residues of veterinary drugs without ADI/MRL", convened in Bangkok in 2004, and an FAO/RIVM/WHO Workshop, "Updating the principles and methods of risk assessment: maximum residue levels (MRLs) for pesticides and veterinary drugs", held in Bilthoven, The Netherlands in 2005. Subsequently this led to the publication of EHC 240, "Principles and methods for the risk assessment of chemicals in food", in 2009. The Codex Committee on Residues of Veterinary Drugs in Foods considered a report of a working group on residues of veterinary drugs without ADI/MRL at their sixteenth session, in Cancun, Mexico, in 2005.

This issue was raised at the sixty-sixth JECFA (February 2006), together with a number of related activities. The Committee concluded that there was need for an overarching approach, and recommended that the JECFA Secretariat convene a working group to develop a decision tree for the evaluation of veterinary drugs. This led to the development of a "Decision tree approach for the safety evaluation of residues of veterinary drugs", which was discussed at the seventieth meeting of JECFA (October 2008). The approach was endorsed by the Committee and a number of revisions suggested. The paper was revised accordingly and submitted as a "Risk-based decision tree approach for the safety evaluation of veterinary drugs" to CCRVDF for its eighteenth session (May 2009), as a work-in-progress. CCRVDF agreed with the proposed general principles and supported further work on the approach.

The scheme was discussed at the seventy-fifth meeting of JECFA (November 2011) and a number of follow-up actions were recommended. However, these were not taken up immediately, due to resource limitations. The seventy-eighth JECFA (November 2013) reiterated the recommendations, which included the establishment of an e-working group to develop guidance for establishing ARfDs for residues of veterinary drugs. This was done, and guidance has been developed and adopted by JECFA (2017), including approaches for the establishment of a microbiological ARfD (mARfD).

A number of other recommendations to further develop the decision tree were made by the seventy-eighth JECFA (2013), which included undertaking work on "preliminary risk assessment", and on the feasibility of using a threshold of toxicological concern (TTC) approach for residues of veterinary drugs. These were not followed up. A number of sections in the draft document noted that further extensive work was required. This included characterization of dietary exposure and management of risk. Since then, much work has been undertaken on dietary exposure assessment, but consideration has yet to be given to how this might be integrated into the decision tree. Guidance on some parts of the scheme

was developed but has yet to be adopted by JECFA, such as on the identification of strengths and weaknesses in the risk assessment (uncertainties and sensitivity analysis).

The present Committee discussed the decision tree and concluded that there is a continuing need for such an approach. It was agreed that the approach should be finalized and published as guidance for JECFA. There was a need to develop some aspects further. There may be a need to include some additional aspects and there may be others that can be omitted. The Committee noted that the approach was essentially generic and would be applicable to additional committees that provide advice to the Codex Alimentarius on food safety, such as JMPR.

A recommendation by the Committee concerning the risk-based decision tree approach for the safety evaluation of residues of veterinary drugs is provided in Annex 3.

**General considerations for microbiological effects**

The impact of drug residues on the human intestinal microbiome is evaluated through a decision tree approach adopted by the sixty-sixth meeting of the Committee, which complies with VICH GL36(R). This entails answering three questions to determine the need for establishing a microbiological acceptable daily intake (mADI). Determine first, if the drug residue, and/or its metabolites, are microbiologically active against representatives of the human intestinal microbiota. Secondly, determine if the drug residues enter the human colon, and thirdly, if the residues entering the human colon remain microbiologically active. If the answer to any of these questions is “no”, then there is no need to calculate an mADI and the assessment does not need to be completed. However, if an mADI needs to be calculated, two end-points of concern for human health are considered for the assessment: disruption of the colonization of the human intestinal microbiome, and increases in populations of resistant bacteria in the human intestinal microbiome. More recently, this was extended to consider the possibility of acute effects and the need for a microbiological ARfD (mARfD).

This guidance delineates a step-by-step approach and provides an explanation of test systems that sponsors can use to address the impact of animal drug residues on the human intestinal microbiome, as another toxicological target of concern.

When JECFA assesses the potential effects of residues of a veterinary drug on humans, the different toxicological targets of concern need to be addressed (reproductive, mutagenesis, carcinogenesis, and chronic toxicity, for example), either by information available in the public domain or by conducting a corresponding study. Because traditional toxicological studies have been done routinely for many years, it is readily understood that all these end-points need to be addressed. However, in the case of the effects of drug residues on the human intestinal microbiome, such a requirement is not so evident since it is only in the last few years that an understanding about the importance of the human intestinal microbiome to human health has become apparent. The human intestinal microbiome is now considered an additional target organ, in which changes in the composition and function of these intestinal microbes (microbiota dysbiosis) has been associated with diseases ranging from localized gastroenterologic disorders to neurologic, respiratory, metabolic, hepatic and cardiovascular illnesses.

Thus, as one more toxicological target of concern, sponsors of drugs submitted for evaluation will need to address the effects of residues on the human intestinal microbiome, for both end-points of concern; the disruption of the colonization barrier and an increase in bacterial resistance. A drug, or its metabolite, might not be an antimicrobial but could still produce disruption and/or increase the population of resistant bacteria, to the extent that an mADI and/or mARfD need to be calculated.

Therefore, sponsors need to fully address both of these concerns for potential impact of drug residues on the human intestinal microbiome, either using information available in the public domain or by running a corresponding study.

Furthermore, while current assessments consider only bacteria in the evaluation, it is now well established that the intestinal microbiome also includes bacteriophages and other viruses, archaea, fungi and protozoa, which play an important role in human health. JECFA will therefore consider how the impact of residues on some or all of the other components of the human intestinal microbiome might be addressed.

A recommendation by the Committee concerning general considerations for microbiological effects is provided in Annex 3

## Annex 3

## *Future work and recommendations*

### Imidacloprid

*Additional Information that would assist in the further evaluation of the compound:*

Further information on disruption of the colonisation barrier and on the selection for, and emergence of, resistance in the microbiota in the gastrointestinal tract.

### Selamectin

*Further information required to complete the residue assessment*

Full registration in a Member State, including GVP.

### Estimation of dietary exposure to veterinary drug residues as performed by JECFA

With the availability of food consumption information expressed on a body weight basis, it is recommended that these data be used preferentially to minimize the assumptions made in deriving the GECDE. It is further recommended that the population groups for which GECDE estimates are derived be amended to align with the age classes currently used in CIFOCOss: infants and toddlers (0–35 months), children and adolescents (3–14 years), and adults and the elderly (15 years and above). It is further recommended that JMPR and JECFA continue to take opportunities to harmonize procedures for dietary exposure assessment.

### A risk-based decision tree approach for the safety evaluation of residues of veterinary drugs

The Committee recommends that the Joint Secretariat, together with other secretariats as appropriate, convene an electronic working group comprising experts from the three committees under JECFA, JMPR, and in dietary exposure assessment, to further develop the decision tree approach, with a view to its finalization in 2023 or 2024.

### General considerations for microbiological effects

The Committee recommends that the Secretariat convene a microbiome expert working group to explore developments in this evolving area.

## Annex 4

### Ninety-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives

Virtual meeting, 16–27 May 2022

**World Health Organization (WHO) members**

Professor (Emeritus) Alan R. Boobis, National Heart and Lung Institute, Imperial College London, London, United Kingdom (*Chairperson*)

Professor Silvana Lima Górniak, Department of Pathology, School of Veterinary Medicine and Animal Sciences, University of São Paulo

**Food and Agriculture Organization of the United Nations (FAO) members**

Dr Alan Chicoine, Department of Veterinary Biomedical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Canada (*Vice-Chairperson*)

Mr Peter Cressey, Senior Scientist, Institute of Environmental Science and Research Limited, Christchurch Science Centre, Christchurch, New Zealand

Dr Holly Erdely, Residue Chemistry Team, Division of Human Food Safety, FDA Center for Veterinary Medicine, Rockville, United States of America (*FAO Rapporteur*)

Dr Rainer Reuss, Safe Work Australia, Canberra, Australia

Professor Susanne Rath, University of Campinas, Department of Analytical Chemistry, São Paulo, Brazil

**FAO experts**

Dr Anke Finnah, German Federal Office of Consumer Protection and Food Safety, Berlin, Germany

Mr Samuel Fletcher, United Kingdom Veterinary Medicines Directorate, Surrey, United Kingdom

Professor Fernando Ramos, University of Coimbra, Faculty of Pharmacy, Coimbra, Portugal

Professor Jae-Han Shim, Distinguished Research Emeritus Professor, Chonnam National University, Gwangju, Republic of Korea

**WHO experts**

Dr Mayumi Ishizuka, Laboratory of Toxicology, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan

Professor Angelo Moretto, Department of Thoracic, Vascular and Public Health Sciences, University of Padova, Padova, Italy (*WHO Rapporteur*)

Dr Silvia A. Pineiro, Ceter for Veterinary Medicine, US Food and Drug Administration, Rockville, MD, United States of America

**FAO Resource contributors (not present at meeting)**

Professor Benjamin U. Ebeshi, Department of Pharmaceutical and Medicinal Chemistry, Niger Delta University, Bayelsa State, Nigeria

Professor Jianzhong Shen, Dean of College of Veterinary Medicine, China Agricultural University, Beijing, People's Republic of China

**Secretariat**

Dr Vittorio Fattori, Food Systems and Food Safety Division, Food and Agriculture Organization of the United Nations (*FAO Secretariat*)

Ms Ngai Yin Ho, Department of Nutrition and Food Safety (NFS), World Health Organization (*WHO Consultant*)

Dr Markus Lipp, Food Systems and Food Safety Division, Food and Agriculture Organization of the United Nations (*FAO Secretariat*)

Mr Soren Madsen, Department of Nutrition and Food Safety (NFS), World Health Organization (*WHO Secretariat*)

Dr Russell Parry, Shrewsbury, United Kingdom (*WHO Editor*)

Dr Moez Sanaa, Department of Nutrition and Food Safety (NFS), World Health Organization (*WHO Secretariat*)