Food and Agriculture Organization of the United Nations

World Health Organization

Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs

Final Report

including

Report of Stakeholder Meeting

7–11 November 2011

Rome, Italy

WHO Library Cataloguing-in-Publication Data

Joint FAO/WHO expert meeting on dietary exposure assessment methodologies for residues of veterinary drugs: final report including report of stakeholder meeting.

1.Food contamination – analysis. 2.Drug residues – analysis. 3.Veterinary drugs – toxicity. 4.Veterinary drugs – adverse effects. 5. I.World Health Organization. II.Food and Agriculture Organization of the United Nations.

ISBN 978 92 4 156449 6 (NLM classification: WA 701)

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List of acronyms and abbreviations

ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
EDI	estimated daily intake
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria monograph
FAO	Food and Agriculture Organization of the United Nations
GEADE	global estimated acute dietary exposure
GECDE	global estimated chronic dietary exposure
GEMS/Food	Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme
IEDI	international estimated daily intake
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOD	limit of detection
LOQ	limit of quantification
MRL	maximum residue limit
STMR	supervised trials median residue
TMDI	theoretical maximum daily intake
USA	United States of America
WHO	World Health Organization

1. Introduction

At the seventieth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Committee discussed a hypothesis-driven decision-tree approach for the safety evaluation of residues of veterinary drugs in foods (FAO/WHO, 2009a). This approach had been developed by a small working group, in response to recommendations of the sixty-sixth JECFA (FAO/WHO, 2006b), and considered the output of a workshop on maximum residue limits (MRLs) in pesticides and veterinary drugs (FAO/WHO, 2006a). As part of the discussion, the Committee identified that further work was required on approaches for exposure assessments for veterinary drug residues in foods, in particular for chronic and acute exposures, for integration into the decision-tree approach.

At its Nineteenth Session in Burlington, Vermont, United States of America (USA), held from 30 August to 3 September 2010, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) requested that FAO and WHO convene an expert consultation on exposure assessment methodologies for residues of veterinary drugs in foods (FAO/WHO, 2010a). This request was a reiteration of the request made at the Eighteenth Session of CCRVDF (FAO/WHO, 2009b). CCRVDF requested that FAO and WHO address the following:

- review of the current "model diet" (also called the "market basket" or "food basket" approach) applied by JECFA;
- possible simplification of the current model diet;
- possible development of several model diets to reflect regional differences in consumption patterns; and
- development of approaches for acute and subchronic[1] dietary exposure assessment.

To help address this need for updated methodology, FAO and WHO issued a call for data on the consumption of foods of animal origin (FAO/WHO, 2010b). To provide an opportunity for stakeholders and interested parties to present their views, FAO and WHO held an open stakeholder meeting in Rome on 7 November 2011. The stakeholder meeting was attended by members of a meeting of experts convened to review and update the principles and methodology to assess dietary exposure to residues of veterinary drugs, held in Rome from 7 to 11 November 2011 (see list of participants in Annex 1), as well as participants at the seventy-fifth meeting of JECFA (see Attachment 2 of Annex 2). The key findings, concerns and recommendations presented by the stakeholders with respect to potential changes to the way in which dietary exposure assessments are currently conducted by JECFA (see Annex 2) were provided to the participants of the meeting of experts to be considered in their discussions. It should be noted that the methods proposed by the meeting of experts were not presented at the stakeholder meeting.

The key objectives of the meeting of experts were twofold:

1) to summarize data recently submitted to FAO and WHO on the consumption of food products derived from animal sources and to compare these data with the existing levels

[1] For the purposes of this report, subchronic and chronic exposures are included together under the term "chronic exposure".

of food consumption in the model diet currently used by JECFA to estimate dietary exposure to veterinary drug residues; and

2) to outline a proposed new approach for estimating dietary exposure to veterinary drug residues for consideration by JECFA that is consistent with approaches to dietary exposure assessments used in risk assessments at an international level for other food chemicals and is appropriate for use in acute and chronic dietary exposure assessments for veterinary drug residues.

The exploration of new approaches to the assessment of dietary exposure to veterinary drug residues is part of the ongoing process of ensuring that evaluations undertaken by JECFA incorporate recent advances in methodology and scientific knowledge. This report proposes a new approach to dietary exposure assessment for veterinary drug residues and is not intended to describe the full process for deriving MRLs for veterinary drug residues.

1.1 Declarations of interest

The experts completed the standard WHO form for declaration of interests prior to the meeting. At the start of the meeting, all participants were asked to confirm their interests and to provide any additional information relevant to the subject matter of the meeting. All experts were reimbursed for their travel expenses by FAO. Dr Baines is part of the regulatory process to establish food standards for veterinary drugs for Australia and New Zealand. Similarly, Dr Edwards and Dr Friedlander contribute to the food chemical risk assessment for the United States Food and Drug Administration. Dr Tennant, Dr Leclercq and Dr Dutra Caldas declared no potentially conflicting interests relevant to the subject matter of the meeting. It was therefore determined that there were no actual or potential conflicts of interest, among any of the participants, of relevance to the subject of the meeting.

2. Background

The first meeting of JECFA devoted exclusively to veterinary drugs was held in 1987 (the thirty-second meeting of JECFA), one of the specific tasks of the Committee being to establish principles for evaluating the safety of residues of veterinary drugs in food (FAO/WHO, 1988).

A chemical risk assessment is usually defined as the likelihood of an adverse health effect occurring given a characterization of the potential adverse health effects and the human exposure to the chemical hazard. The principles and methods for the risk assessment of chemicals in food are described in a recent FAO/WHO monograph (FAO/WHO, 2009c). By convention, the risk assessment process for food chemicals has been divided into four steps: 1) hazard identification; 2) hazard characterization/dose–response assessment; 3) exposure assessment; and 4) risk characterization.

The first two steps lead to the identification of a health-based guidance value that establishes the maximum level of exposure that is acceptable for a particular food chemical; examples include the upper bound of an acceptable daily intake (ADI) and an acute reference dose (ARfD). The health-based guidance value for veterinary drug residues traditionally established by the Committee is the ADI: the estimated amount of a substance in food or drinking-water, expressed on a body weight basis, that can be consumed every day for a lifetime by humans without presenting an appreciable risk to their health (FAO/WHO, 2009c). On rare occasions, the Committee has established ARfDs for veterinary drug residues.

The third step of the risk assessment process as applied to veterinary drug residues is to assess exposure to veterinary drug residues from the diet, undertaken by combining food consumption data with residue data. The resultant estimated dietary exposure can then be compared with the relevant health-based guidance value in the fourth step of risk assessment, the risk characterization step.

2.1 Development of the current model diet

JECFA developed a model diet (or standard food basket) for use in dietary exposure assessments for veterinary drug residues. The model diet was intended to provide a conservative estimate of dietary exposure. Initially (at the thirty-second meeting), the Committee used a model diet of 500 g of meat for the purposes of assessing dietary exposure to veterinary drug residues (FAO/WHO, 1988). At the thirty-fourth meeting of JECFA, the diet was revised to include amounts of other raw commodities, such as offal, fish, eggs and milk. The 500 g meat was divided into 300 g muscle, 100 g liver, 50 g kidney and 50 g tissue fat; and 100 g egg and 1.5 litres of milk were added (FAO/WHO, 1989). At later meetings, honey was added to the model diet, and fish muscle with skin in natural proportions was identified as an alternative to meat. The food consumption amounts, assumed to be consumed daily by a 60 kg person, were chosen from available information to represent the upper limit of the range of consumption for individual edible tissues and animal products (including processed foods with animal products as ingredients) eaten daily over a lifetime (i.e. chronic exposure).

Hence, it was assumed that the same diet could be used to cover both potential acute (short-term) exposure as well as chronic (long-term) exposure.

The model diet was reviewed at the fortieth meeting of JECFA (FAO/WHO, 1993), the Committee noting that the type of food consumption data used to derive the model diet had been derived from different sources, such as food balance sheet data and dietary survey data, which were not directly comparable. The Committee reaffirmed the position of the thirty-fourth meeting (FAO/WHO, 1989) that the food consumption values in the model diet were adequately conservative.

Dietary exposure estimates based on the model diet were considered conservative because it was assumed that the food consumption amounts were maximum values, that all animals used as food were treated with the veterinary drug and that all foods produced from these animals contained the drug residue at a given concentration. For the purposes of chronic dietary exposure assessment, it was also assumed that these food amounts were consumed daily over a lifetime. Initially, the residue concentration used in the dietary exposure assessment by the Committee was the MRL for each commodity in the model diet, with a correction for the ratio of the concentration of the marker residue to that of the total residue. The resultant dietary exposure estimate was termed the theoretical maximum daily intake (TMDI). The MRL is derived from depletion studies when sufficient data are available to establish a depletion curve for a specific tissue. It is defined as a point concentration of the marker residue on the residue depletion curve describing the upper one-sided 95% confidence limit over the 95th percentile (FAO/WHO, 2009c), with all appropriate tissue MRLs based on the same time point (the time of slaughter consistent with good practice in the use of veterinary drugs, i.e. the withdrawal time). In a limited number of instances, where insufficient quantifiable values (i.e. fewer than four values) were available to derive an MRL using this approach, alternative, more approximate methods were used. If the TMDI exceeded the ADI, the MRL was readjusted to ensure that the TMDI remained at or below the ADI.

The calculation of a TMDI for colistin (ADI = 0–420 µg/person) is given as an example in Table 1.

Table 1. Example calculation of a TMDI: colistin

Food	MRL (µg/kg)[a]	Consumption value (kg/person per day)	Marker/total[b]	Dietary exposure (µg/person per day)
Muscle	150	0.3	0.8	56
Liver	150	0.1	0.8	19
Kidney	200	0.05	0.8	13
Fat	150	0.05	0.8	9
Milk	50	1.5	0.8	94
Eggs	300	0.1	0.8	38
TMDI				229
ADI (upper bound)				420

[a] The MRLs for all target tissues and eggs were based on twice the limit of quantification of the analytical method. The tissue MRLs were the same for all species.

[b] The colistin residues were measured by a microbiological method that does not report all relevant residues. As the marker residue colistin A + B represents approximately 80% of the microbiologically active residues, the marker/total ratio of 0.8 is incorporated into the calculation of dietary exposure estimates to ensure that they correctly reflect residues of microbiological concern.

The use of the median residue concentration, instead of the MRL, was introduced at the sixty-sixth meeting of JECFA (FAO/WHO, 2006b). During that meeting, the Committee agreed that the median concentration represents the best point estimate of a central tendency over a prolonged period of time because the concentration of residues in a given tissue consumed varies from day to day, as reflected in the distribution. At the seventieth meeting of JECFA (FAO/WHO, 2009a), the Committee reaffirmed the use of the median residue concentration from depletion studies, with a correction for marker/total residues, for chronic dietary exposure estimates; the resultant dietary exposure estimate using the median residue concentration is termed the estimated daily intake (EDI). During the Expert Meeting, the experts recognized that the distribution of residues is unlikely to be normal, but agreed to use the median residue concentration to estimate long-term dietary exposure. The use of the median residue concentration was restricted to chronic dietary exposure estimation and where there were adequate data.

The experts noted that a recent European Food Safety Authority (EFSA) document on handling concentration data below the limit of detection (LOD) in dietary exposure assessment recommends estimating both the lower bound (non-detects replaced by 0) and the upper bound (non-detects replaced by the LOD). If the discrepancy between the two values is significant, EFSA recommends that both of them be reported (EFSA, 2010). However, results below the LOD or limit of quantification (LOQ) are typically assigned a value of one half of the respective limit when calculating the median residue concentration.

The EDI calculation, where "muscle" refers to either meat or fish, is as follows:

$$\begin{aligned}\text{EDI} = {} & (300\ \text{g} \times \text{median residue}_{\text{muscle}}) + (100\ \text{g} \times \text{median residue}_{\text{liver}}) + (50\ \text{g} \times \text{median residue}_{\text{kidney}}) + \\ & (50\ \text{g} \times \text{median residue}_{\text{fat}}) + (100\ \text{g} \times \text{median residue}_{\text{eggs}}) + (1500\ \text{g} \times \text{median residue}_{\text{milk}}) + \\ & (50\ \text{g} \times \text{median residue}_{\text{honey}})\end{aligned}$$

The calculation of an EDI for the antimicrobial colistin (ADI = 0–420 µg/person) is given as an example in Table 2. As the median residue value for an edible commodity such as muscle may vary between different food-producing species, it is important, when reporting, to identify the relevant species for each of the edible commodities. For each food commodity, the highest species-specific median residue value is used in the calculation.

At the seventieth meeting of JECFA (FAO/WHO, 2009a), it was again noted that the use of the EDI was applicable only to chronic dietary exposure assessments. JECFA to date has not developed principles for acute dietary exposure assessments.

2.2 Concerns raised about the use of the model diet

One of the major concerns raised about the use of the model diet has been that it is overly conservative for a chronic dietary exposure assessment.

At the Nineteenth Session of CCRVDF (FAO/WHO, 2010a), a report from a working group (led by France) that was tasked with consideration of all relevant factors in the MRL setting process noted that consumers are not likely to be ingesting high amounts of different animal products simultaneously. Hence, a limited number of target tissues consumed in large amounts may be used for a model diet. One suggested option was to consider a modified model diet of "one meat + two eggs + milk + honey", an approach currently used in the USA, which could be used without changing the foods listed in the present standard model diet. It was also noted that the EDI was applicable only for substances exhibiting chronic toxicity.

Table 2. Example calculation of an EDI: colistin[a]

Food	Median residue (µg/kg)[b]	Consumption value (kg/person per day)	Marker/total[c]	Dietary exposure (µg/person per day)
Muscle (turkey)	38	0.3	0.8	14.3
Liver (pigs)	38	0.1	0.8	4.8
Kidney (rabbits)	145	0.05	0.8	9.1
Fat (rabbits)	82	0.05	0.8	5.1
Milk (cattle)	11	1.5	0.8	20.6
Eggs (chickens)	24	0.1	0.8	3.0
EDI				56.9
ADI (upper bound)				420

[a] It should be noted that this example was selected because data were available from a recent JECFA evaluation, even though the ADI for colistin was based on an acute end-point. The goal of the exercise was to compare the outcomes of different approaches to estimating dietary exposure with the ADI, not to discuss the hazard characterization.

[b] In this example, the median values for each target tissue and eggs were taken from the species with the highest tissue-specific median residue value.

[c] The colistin residues were measured by a microbiological method that does not report all relevant residues. As the marker residue colistin A + B represents approximately 80% of the microbiologically active residues, the marker/total ratio of 0.8 is incorporated into the calculation of the dietary exposure estimates to ensure that they correctly reflect residues of microbiological concern.

This working group did consider as an option the use of regional diets for chronic dietary exposure assessment, as put forth by CCRVDF for consideration by the FAO/WHO Expert Meeting (FAO/WHO, 2010a), but in the end proposed an alternative approach.

During its discussions of the β-agonist ractopamine, a veterinary drug that may be found in lung as well as other tissues, the Nineteenth Session of CCRDVF also noted that data on consumption of lung tissues were lacking in the model diet (FAO, 2010; FAO/WHO, 2010a). It was noted that tissues such as lung or intestine had been reported to be consumed in countries such as China. In recommending that a meeting of experts be held on dietary exposure assessments for veterinary drugs, CCVRDF noted that the meeting should consider enlarging the scope of the model diet to include other target tissues (FAO/WHO, 2010b).

The Expert Meeting also recognized the need to consider the objectives of the project to update the principles and methods for the risk assessment of chemicals in food when reviewing the model diet. These objectives were to harmonize (as appropriate) 1) the risk assessment procedures for different classes of chemicals in food (e.g. additives, contaminants, pesticide residues, veterinary drug residues and natural toxicants) and 2) the approaches to risk assessment by JECFA and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) with those of other scientific groups (e.g. national, regional, public health, environmental) (FAO/WHO, 2009c).

3. Summary of food consumption data submitted

In order to assess whether the food consumption amounts used in the current model diet were overly conservative for the purpose of undertaking a chronic dietary exposure assessment or were suitable for the purpose of undertaking an acute dietary exposure assessment, it was necessary to obtain up-to-date food consumption data from Member countries.

A request for food consumption data for standard and non-standard animal tissues and food of animal origin was issued by FAO and WHO on 26 October 2010 (FAO/WHO, 2010b). Forty-seven countries submitted data in response to this request. For some countries, more than one data set was submitted.

A variety of methods were used to collect these data, as summarized in Annex 3:

- Individual-level survey data were submitted by 24 countries, including Argentina, Australia, Brazil, Cambodia, China, Thailand, Viet Nam, the USA and 21 European countries summarized in the EFSA Comprehensive European Food Consumption Database.
- Household budget survey data were submitted by Brazil and Cameroon.
- Food balance sheet data were submitted by 17 Latin American countries. Two countries (Argentina and Brazil) that submitted food balance sheet data also submitted individual-level survey data.[1]

The type of food consumption data sets submitted varied, also summarized in Annex 3:

- *Population group*: Mean consumption for the total population (consumers and non-consumers) only and/or means, medians and high percentiles (95th, 97.5th and/or 99th percentiles) for consumers only and the total population were provided.
- *Food amounts reported*: Food amounts were expressed on an *as consumed* basis (i.e. cooked or otherwise prepared for consumption) and/or on a *raw weight* basis (converted from as consumed).[2]
- *Large portion size*: Survey data were typically expressed on a person-day basis for acute data and on an average per day basis for chronic data; however, sometimes data were provided only on an average per day basis.
- *Survey duration*: Survey duration ranged from 1 day (nine countries) to 7 days (five countries), with one country submitting data from a 15-day survey of household expenditures. The majority of surveys were of 2–3 days' duration and used 24-hour recall or food record methods.
- *Age group*: Data were available for the specific population of children aged 2–6 years from a subset of countries (Australia, China, USA), and EFSA compiled data for infants (<1 year), toddlers (ages 1–3 years) and other children (ages 3–9 years). For the purposes

[1] Per capita food balance sheet data apply to the total population (all ages) within a particular country and represent the total amount of food available for consumption in a given year (food produced plus imports minus exports and non-food use, sometimes adjusted for waste) divided by the total population and adjusted to a per person per day basis.

[2] Conversion factors would need to be applied to convert food consumption data provided on an *as consumed* basis to a *raw weight* basis for appropriate comparison of data sets.

of this exercise, EFSA data for children that best fitted the 2- to 6-year age group were evaluated. Surveys from some other countries reported data only for people aged 2 and over (2+) or for adults only, which was defined differently in different countries. For the purposes of this exercise, general population data for ages 2+ were compiled from available data for ages 2+ and data for adults, if no other data were submitted from a particular country. It was decided to include adults-only data, as they provided a conservative but generally similar estimate of food consumption amounts to that for populations aged 2+, with the possible exception of milk consumption. No additional weightings were applied to account for undersampling or oversampling of certain ages within a given survey.

- *Individual body weight correction*: Of the countries that submitted either individual or household survey data, 26 countries provided food consumption data corrected for each individual's body weight, and 6 countries provided uncorrected data. Six of the 26 countries provided body weight–corrected data based on 1-day surveys; hence, these data sets could be used for acute but not chronic dietary exposure estimates. Individual body weights per se were not submitted.

4. Proposed approach to dietary exposure estimates for veterinary drug residues

4.1 General considerations

Dietary exposure assessment combines food consumption data with data on the concentration of chemicals in food. The resulting dietary exposure estimate may then be compared with the relevant health-based guidance value for the food chemical of concern, if available, as part of the risk characterization. Assessments may be undertaken for acute or chronic exposures, where acute exposure covers a period of up to 24 hours and chronic or long-term exposure covers average daily exposure over the entire lifetime.

The general equation for both acute and chronic dietary exposure is:

$$\text{Dietary exposure} = \frac{\Sigma\ (\text{Concentration of chemical in food} \times \text{Food consumption})}{\text{Body weight}}$$

for all foods containing the residue.

The Environmental Health Criteria (EHC) monograph on *Principles and methods for the risk assessment of chemicals in food* (FAO/WHO, 2009c), referred to hereafter as EHC 240, recommends certain general principles and considerations when undertaking dietary exposure assessments. These principles were considered when developing proposed methods for the assessment of acute and chronic exposures to veterinary drug residues in food. In particular, the current approach considered the following:

- With regard to the proposed dietary exposure methods, similar methods appropriate for contaminants, pesticides, food additives (including flavourings), processing aids and other chemicals in foods were considered.
- No screening methods were proposed, because it was considered unlikely that a high number of substances would need to be assessed.
- Dietary exposure assessment methods used at an international level use residue data from trials and depletion studies. These studies tend to be well controlled but of small sample size and may not reflect residue concentrations resulting from actual use of a pesticide, food additive or veterinary drug. In the future, more refined estimates could be made in addition to these more conservative estimates if residue data based on a sufficient number of samples collected by monitoring and surveillance programmes in individual countries were made available to JECFA. However, for dietary exposure estimates, random representative data, which provide an indication of actual residue concentrations to which consumers are exposed, are preferred to data from targeted surveys, which are considered unlikely to be representative of the food supply available.
- Data from the Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food), both the consumption cluster diets (http://www.who.int/foodsafety/chem/gems/en/index1.html) and the large portion size database (http://www.who.int/foodsafety/chem/gems/en/index2.html), were evaluated as a source of food consumption data, in addition to the submitted data.

- For both acute and chronic dietary exposure estimates, food consumption data derived from surveys conducted at the individual level should ideally be used to provide a realistic representation of people's actual consumption patterns.
- Methodologies should take into consideration non-average individuals, such as those who consume large portions of specific food items, as recommended in EHC 240.
- International dietary exposure assessment methods should provide exposure estimates that are equal to or greater than the best available (i.e. most accurate) estimates carried out at a national level, to ensure sufficient conservatism. It is assumed that the international estimate covers potential dietary exposure in countries for which no data are available.
- Possible population subgroups of concern were considered. It was decided to include separate data on infants and children, because the amount of food they consume in relation to body weight is higher than for older age groups, and the composition of people's diets changes as they age. Infants and young children may, for example, be more dependent on particular commodities such as milk than are people in other age groups. The proposed approach to dietary exposure assessments therefore covers the general population as well as groups that are potentially vulnerable or are expected to have dietary exposures that are significantly different from those of the general population. It is recognized that infants and young children have energy and nutrient intake requirements met by food consumption that, when expressed per kilogram body weight, are higher than those for older children due to their higher requirements for both growth and body maintenance. Infants aged 0–3 months and children aged 2–6 years were taken to represent the most conservative cases of potentially vulnerable subpopulation groups: infants aged 0–3 months because milk (breast milk or infant formula) is their sole source of nutrition; and children aged 2–6 years due to higher total food consumption per kilogram body weight than for any other age group in the population.

4.2 Acute dietary exposure assessments

Acute dietary exposure estimates cover a time period of food consumption over a single meal or 24 hours and are intended to be used for comparison with ARfD values in a risk assessment process (FAO/WHO, 2009c). Hence, the need for an acute dietary exposure assessment will depend (to some extent) on whether an ARfD for the residue has been established.

The ***proposed acute dietary exposure model*** considers high-level exposure from each relevant food of animal origin singly—that is, the concurrent occurrence of the selected high residue concentration in each food to which a consumer might be exposed (e.g. MRL or high residue concentration derived from depletion studies, such as the upper one-sided 95% confidence limit over the 95th percentile residue concentration) combined with a high daily consumption (97.5th percentile) of that food (meat, offal, milk, others).

The global estimated acute dietary exposure, or GEADE, is calculated as follows:

$$\text{GEADE} = \frac{\text{97.5th percentile food consumption (1 person-day)} \times \text{High residue}_{\text{tissue}}}{\text{Body weight}}$$

The 97.5th percentile food consumption amount (consumers only) was selected because it is statistically a more robust value than the maximum food consumption amount, as the latter is a single value and may not best represent the actual distribution of values. The Expert Meeting noted that this approach (i.e. foods assessed singly using the 97.5th percentile food

consumption amount and a high residue concentration) was consistent with that used by JMPR for acute dietary exposure assessments for pesticides. There is also an extensive GEMS/Food large portion size database available with 97.5th percentile consumption values for raw commodities of animal origin.

It is noted that for raw commodities subject to mixing before sale and consumption or subject to further processing, such as milk, oils and grains, the supervised trials median residue (STMR) concentration is considered by JMPR to be an appropriate residue value for acute assessments for pesticide residues (FAO/WHO, 2009c). However, as milk may not be mixed prior to consumption or use in the production of dairy products in all countries, the Expert Meeting decided to take a more conservative approach and use the selected high residue concentration in the acute dietary exposure assessment for veterinary drug residues in milk.

It is possible that, in a single meal or over 1 day, a person could have background exposure to the veterinary drug residue from other foods consumed in that time period in addition to high levels of exposure from a single food. However, the acute exposure estimate is conservative in that it assumes that the single food contains a high residue concentration, which monitoring data indicate is unlikely to be actually found in the food supply. It was therefore assumed that the estimated dietary exposure from a single food would be a much higher value than the level of background exposure and that inclusion of background exposure in the estimate would not substantially improve the accuracy of the estimate. However, the Expert Meeting noted that this assumption needs to be further investigated.

In the risk characterization stage of a risk assessment, the GEADEs for all relevant foods for the general population, children aged 2–6 years and infants (milk only, assumed to be infant formula) would be compared with the health-based guidance value for acute toxicity (ARfD). If any one of these estimates exceeded the ARfD, then the assumptions underlying the risk characterization would first be re-evaluated before determining if there may be cause for concern.

4.3 Chronic dietary exposure assessments

Chronic dietary exposure estimates cover food consumption over the long term and are intended to be used for comparison with a health-based guidance value based on chronic toxicity, such as an ADI, in a risk assessment process (FAO/WHO, 2009c).

For most regulatory purposes for food chemicals, as recommended in EHC 240, non-average individuals who may consume one or more foods in higher than average amounts over a long period of time should also be considered in the risk assessment. The Expert Meeting noted that the use of mean food consumption data for the total population (consumers and non-consumers of the foods containing veterinary drug residues) as a basis for chronic dietary exposure assessments would exclude habitual consumers of specific food categories (FAO/WHO, 2009c).

In one simple approach designed to account for the habitual high consumer (originally described by Verger, 1995; see also Counil, Verger & Volatier, 2006), the 95th percentile dietary exposure (calculated considering consumers only) from each relevant food category is added to the mean dietary exposure from all other foods (consumers and non-consumers) in the diet to estimate the total dietary exposure of high-level consumers of each food type. The highest of these estimates is then selected for use in the risk assessment. This approach has

been used for estimating intakes of food and feed additives and nutrients from food (Tennant, Becquet & Jans, 2009).

A more conservative version of this approach consists of summing the 95th percentile of exposure for the two highest categories that are the main contributors with the mean exposure for the other categories (EFSA, 2008). The method employing the two highest individual foods is applicable to situations in which chemicals are likely to be present in a diverse number of food categories that may be consumed at a high level by the same individuals. In addition, it is important to note that this method is only valid when using a small number of broad food groups (around 20 food groups). However this method is not acceptable when using a database containing a higher number of food categories (around 160 food groups). If foods are defined at a high level of disaggregation (it is possible for one person to consume up to eight or nine foods at a high level over a period of time (EFSA, 2011).

Based on research undertaken prior to the Expert Meeting into the use of different approaches (see Annex 4) for veterinary drug residues that are solely found in a limited number of food groups, including only foods of animal origin, it was considered overly conservative to assume that even two foods would be consumed at a high level over a long period of time.

The ***proposed chronic dietary exposure model*** for veterinary drug residues assumes that in the longer term, an individual would be a high-level consumer of only one category of food and that his or her consumption of other foods containing the residue would remain at the population average (total population). The Expert Meeting proposed that the 97.5th percentile food consumption amount for consumers only should be used, to be derived from surveys with individual records of 2 or more days' duration by first calculating the average food consumption amount per day per person, preferably expressed on a per kilogram body weight basis for each individual. The choice of a high percentile, such as the 97.5th percentile, was justified by its application for a single commodity (instead of two, as applied for other food chemicals). The 97.5th percentile was proposed because it was more commonly reported in the data submitted. However, the experts recognized that the 90th or 95th percentile can also be considered to represent chronic (regular) high consumption. In any case, it is essential to document information on the number of consumers on which the percentile is based.

It is logical and statistically valid to sum the mean dietary exposure to a veterinary drug residue from each food to estimate the total mean exposure from all foods in the diet for the total population. On the other hand, high-level consumption of different foods relates to different subpopulations of consumers, as not every person reports consumption of all foods each day of a survey. Hence, higher percentiles of food consumption cannot be summed to estimate total high-level food consumption from all foods.

In order to select the single animal product that contributes the highest dietary exposure for a specific veterinary drug residue, the following calculation is undertaken for each food in the diet that has residue values:

High-level exposure from each animal product	=	**97.5th percentile consumption**	×	**Median residue**[1]
(mg/kg body weight per day or mg/day)		(kg/kg body weight per day or kg/day)		(mg/kg)

[1] It should be noted that the median has to be determined based on at least four or five observations; reporting of the 95% confidence interval around the median is advisable.

The global estimated chronic dietary exposure (GECDE) to the veterinary drug residue for the population group of interest is the highest exposure calculated using the 97.5th percentile consumption figure for a single food selected from all the foods plus the mean dietary exposure from all the other relevant foods:

GECDE	=	**Highest exposure from one animal product**	+	**Total mean exposure from all other products**
(mg/kg body weight per day or mg/day)		(mg/kg body weight per day or mg/day)		(mg/kg body weight per day or mg/day)

In most cases, the food with the highest estimate of exposure using the 97.5th percentile consumption value drives the resulting dietary exposure estimate. In the rare case where two foods have similar 97.5th percentile exposure values, the calculation should be undertaken for each one to determine the higher GECDE.

4.4 Data for use in acute dietary exposure assessments

A template was first developed that listed each food of animal origin of interest in evaluations of veterinary drug residues for which data were available to support inclusion in the calculations. From the submitted data and the GEMS/Food large portion size database, the highest 97.5th percentile value for each food was selected. Some of the submitted data were higher than values in the current GEMS/Food database, such as new data from China and Australia. The GEMS/Food database will be updated in the future to incorporate these new data.

When considering food consumption data for acute exposure estimates, one person-day data from surveys with individual records were considered by preference, as recommended in EHC 240 (FAO/WHO, 2009c). For example, for a survey of 2 days' duration, days 1 and 2 were treated as separate records for each individual.

A summary of data compiled by selecting the highest 97.5th percentile value derived from one person-day data from available data sets for use in acute dietary exposure assessments is given in Table 3. In this case, data were available on a gram per person per day basis and a gram per kilogram body weight per day basis (see Annex 3), the latter considered to give a more accurate estimate of exposure when it has been derived using individual body weights. As a result, the food consumption data should be considered provisional until a further data call is made to obtain, where possible, data derived from the original individual records from all countries. Although the data currently available were used for the purpose of this meeting to illustrate the proposed approach, they should not be used in risk assessment by JECFA or risk management by the Codex Alimentarius Commission until they have been finalized and undergone validation. It is noted that some of the 97.5th percentile large portion sizes are greater than the food consumption amounts in the current model diet for the same food category. The values in Table 3 also indicate that the country supplying the highest reported value may change depending on whether grams per person per day data or grams per kilogram body weight per day data are considered. The Expert Meeting noted that it is not appropriate to directly compare the exposure estimate from the current model diet with the GEADEs, as they are based on different assumptions.

Table 3. Large portion size data (97.5th percentile consumption, one person-day data)[a] for use in acute dietary exposure estimate (provisional)

Food type as raw commodity	97.5th percentile, general population, 1 day (g/person per day)	97.5th percentile, general population, 1 day (g/kg body weight per day)[a]	97.5th percentile, children aged 2–6, 1 day (g/person per day)	97.5th percentile, children aged 2–6, 1 day (g/kg body weight per day)[a]
Mammalian muscle				
Beef and other bovines	522 (France)	10 (France)	255 (France)	13.4 (France)
Pork and other porcines	665 (Brazil)	10 (Brazil)	261 (China)[b]	16.2 (China)
Sheep and other ovines	490 (South Africa)	8.8 (South Africa)	262 (China)[b]	16.4 (China)
Goat and other caprines	477 (USA)	7.3 (USA)	76 (USA)	4.2 (USA)[c]
Horse and other equines	525 (China)[b]	9.9 (China)	na	na
Rabbit	419 (China)[b]	7.9 (China)	na	na
All mammalian muscle	559 (Australia)	8.3 (Australia)	254 (Australia)	16.7 (Australia)
Mammalian trimmed fat, skin and added fat	254 (China)[b]	4.8 (China)	65 (France)	3.4 (France)
Mammalian offal				
Mammalian liver	465 (USA)	7.2 (USA)	200 (China)	12.5 (China)[c]
Mammalian kidney	788 (USA)	12.1 (USA)	225 (China)	14.1 (China)[c]
Mammalian lung	300 (China)	5.7 (China)[c]	150 (China)	9.4 (China)[c]
All mammalian offal	524 (South Africa)	9.4 (South Africa)	238 (China)[b]	14.9 (China)
Fish and seafood				
Fish	1200 (Brazil)	19 (Brazil)	315 (China)	19.7 (China)
Crustaceans	747 (Brazil)	11.8 (Brazil)	350 (China)	21.9 (China)
Molluscs	650 (Germany)	14.3 (Greece)	327 (Italy)	7.6 (Germany)
All fish and seafood	600 (Hungary)	8.3 (Bulgaria)	345 (Italy)	14.8 (Italy)
Poultry muscle	535 (China)[b]	10.1 (China)	333 (China)[b]	20.8 (China)
Poultry fat and skin	43 (USA)	0.7 (USA)	15 (USA)	0.8 (USA)
Poultry offal	348 (France)	6.07 (China)	248 (USA)	13.8 (USA)

Food type as raw commodity	97.5th percentile, general population, 1 day (g/person per day)	97.5th percentile, general population, 1 day (g/kg body weight per day)[a]	97.5th percentile, children aged 2–6, 1 day (g/person per day)	97.5th percentile, children aged 2–6, 1 day (g/kg body weight per day)[a]
Eggs (all)	383 (France)	7.3 (France)	201 (France)	12.1 (China)
Milk[d]	2466 (USA)	37.9 (USA)	1933 (Australia)	101.7 (Australia)
Honey	165 (Brazil)	2.4 (Brazil)	43 (Australia)	2.3 (Australia)

na, not available

[a] 97.5th percentiles in grams per kilogram body weight per day were calculated in one of two ways: 1) based on the observed distribution expressed per kilogram body weight; or 2) by dividing the 97.5th percentiles in grams per day by the observed average body weight in the population.

[b] All grams per day data for China have been back-calculated from the grams per kilogram body weight per day data, considering the average body weight provided for that population.

[c] For Chinese data, standard body weights of 53 kg for the general population 2+ years and 16 kg for children aged 2–6 years were used, provided by China; for USA data, body weights of 65 kg for the general population 2+ years and18 kg for children aged 2–6 years were used, provided by the USA.

[d] Includes whole liquid milk, secondary milk products (e.g. skimmed milk, evaporated milk, milk powders), derived milk products (e.g. cream, butter) and manufactured milk products (yoghurt, cheese, ice cream).

4.5 Data for use in chronic dietary exposure assessments

When considering food consumption data for chronic dietary exposure assessments, the duration of the survey from which the food consumption data are derived should be taken into account. For chronic exposure estimates, it is preferable to use surveys of more than 1 day's duration to represent "usual" consumption patterns so that the average food consumption is calculated per day for each individual in the survey over the number of days of the survey before the high percentile is derived from the distribution of food consumption values. The range of distribution therefore tends to decrease towards the central measure the longer the duration of the survey; hence, a 97.5th percentile consumption from a 2-day survey will tend to be lower than that derived from 1-day data and provides a better representation of high chronic consumption; that from a 7-day survey would tend to be lower again.

For exposure estimates based on broad food categories (e.g. muscle or milk) that are likely to be consumed daily by the majority of the population, survey duration is not such a critical issue; in a given population, the amounts of these foods consumed tend not to vary significantly from day to day, so the difference between food consumption estimates from 1 and 2 or more days of data is minimal. Survey duration is much more important when considering foods that are less frequently consumed in some countries, such as liver and kidney, and it is significant to note that these commodities are more likely to contain higher concentrations of veterinary drug residues. For foods such as liver and kidney, the longer the duration of the survey, the more consumers are identified, so that the proportion of the population consuming (% consumers) appears to increase. Conversely, the average amount that a consumer eats (g/day) appears to decline as the survey duration is extended. As the proportion of the population consuming is frequently very small, this makes reliable estimates of long-term consumption of such commodities extremely difficult (see section 6).

From the information submitted, the most comprehensive data sets for high food consumption values were for one person-day 97.5th percentile food consumption values (e.g. GEMS/Food large portion size database). However, some information was available on 97.5th percentile food consumption from surveys of 2 or more days' duration, where the amount of food consumed by each individual in the survey was averaged over the number of days of the survey before the 97.5th percentile for the population group of interest was

derived. This last type of data is more appropriate for use in chronic dietary exposure assessment.

Annexes 5 and 6 summarize data submitted for use in chronic dietary exposure assessments for general populations aged 2 years and over and for children aged 2–6 years, respectively (mean, 97.5th percentile, consumers only, averaged per day over the survey duration where these data were available).

As a conservative approach, the highest reported mean food consumption values of those available for different countries were selected for animal products for the total population (Table 4). The highest 97.5th percentile value derived from surveys with individual records of 2 or more days' duration from available data sets for use in chronic dietary exposure assessments is also given in Table 4 for the general population aged 2 years and over and for children aged 2–6 years. Information from countries reporting food balance sheet data or using a food frequency method to collect data on food consumption were not included in this exercise, although submitted data are still listed in Annexes 5 and 6. These values are therefore considered provisional, as food consumption expressed as grams per kilogram body weight, derived from the original individual records, would be preferred. A further data call is required to obtain these data, to confirm survey duration for some data sets from some countries where this information was not submitted and, if possible, to obtain chronic high-percentile consumption data (i.e. 90th, 95th and 97.5th percentiles) from surveys of 2 or more days' duration where not previously available. Although the data currently available were used for the purpose of this meeting to illustrate the proposed approach, they should not be used in risk assessment by JECFA or risk management by the Codex Alimentarius Commission until they have been finalized and undergone validation.

Food consumption values are currently reported in grams per day. In this case, standard body weight values need to be used to assess exposure per kilogram body weight: 60 kg for adults, 15 kg for children and 5 kg for infants. The same model should be developed where consumption levels are expressed per kilogram body weight per day. The proposed model diet reports levels of consumption at a more disaggregated level by distinguishing mammalian products from poultry products in terms of muscle, offal, fat and skin. Moreover, among mammals, levels of consumption for muscle are provided according to five different categories: beef and other bovines, sheep and other ovines, goat and other caprines, horse and other equines, and rabbit. This is because different residue concentrations may be provided in different species and a more refined exposure assessment may be provided by combining these residue concentrations to the appropriate level of consumption. Similarly, the fish and seafood category is disaggregated into fish, molluscs and crustaceans to allow appropriate combination of residue concentrations with levels of consumption. Where residue concentrations would not be available at a disaggregated level or would be available for species not reported in the list, the overall level of consumption for the category would be used (e.g. "All mammalian muscle", "All fish and seafood").

The levels of consumption considered in the current model diet used by JECFA are higher than the highest average consumption among countries for which data were made available to the Expert Meeting. In the case of milk, the levels of consumption in the current model are also higher than the highest high-level chronic consumption (assessed as the highest 97.5th percentile in consumers only for surveys lasting at least 2 days) among countries for which data were made available to the Expert Meeting. For muscle, the level of consumption in the current model diet (300 g) is lower than chronic high consumption of total mammalian

Table 4. Comparative food consumption data for use in the chronic dietary exposure assessment derived from surveys with individual records of 2 days' duration or more, with food consumption averaged over number of days of survey (provisional)

	Current JECFA model diet for veterinary drug residues	General population[a]					Children[b]				Infants[c]
Food type as raw commodity	(g/person per day)	Mean total population (g/person per day)	*Comments*	Mean total population (highest GEMS/Food cluster) (g/person per day)	High-level chronic consumers (g/person per day)	*Comments*	Mean total population (g/person per day)	*Comments*	High-level chronic consumers (g/person per day)	*Comments*	(g/person per day)
Mammalian muscle											
Beef and other bovines		127	*Highest GEMS/Food cluster, higher than all individual surveys: 97 Brazil, >10 years*	127 (M)	325	*Brazil, 2 days, 97.5th percentile consumers only, 2 days*	39	*Australia, 2–6 years*	88	*USA, 97.5th percentile consumers only, 2 days, 2–6 years*	—
Pork and other porcines		69	*Highest GEMS/Food cluster, higher than all individual surveys*	69 (F)	428	*Brazil, 97.5th percentile, 2 days, consumers only, unpublished data*	25	*Australia, 2–6 years*	90	*USA, 97.5th percentile consumers only, 2 days, 2–6 years*	—
Sheep and other ovines		11	*Highest GEMS/Food cluster; 25 Australia, but 1-day survey only*	11 (B)	373	*Brazil, 2 days, 97.5th percentile consumers only, 2 days*	13	*Australia, 2–6 years*	—	*No chronic consumption reported in any country*	—
Goat and other caprines		5	*Highest GEMS/Food cluster, higher than Brazil household budget survey (0.3), not available in individual surveys*	5 (J)	401	*Brazil, 2 days, 97.5th percentile consumers only, 2 days, unpublished data*	—	*No chronic consumption reported in any country*	—	*No chronic consumption reported in any country*	—
Horse and other equines		2	*Highest GEMS/Food cluster*	2 (M)	—	*No chronic consumption reported in any country*	—	*No chronic consumption reported in any country*	—	*No chronic consumption reported in any country*	—
Rabbit		5	*Highest GEMS/Food*	5 (B)	—	*No chronic*	—	*No chronic*	—	*No chronic*	—

Food type as raw commodity	Current JECFA model diet for veterinary drug residues (g/person per day)	General population[a]					Children[b]				Infants[c]
		Mean total population (g/person per day)	*Comments*	Mean total population (highest GEMS/Food cluster) (g/person per day)	High-level chronic consumers (g/person per day)	*Comments*	Mean total population (g/person per day)	*Comments*	High-level chronic consumers (g/person per day)	*Comments*	(g/person per day)
			cluster			*consumption reported in any country*		*consumption reported in any country*		*consumption reported in any country*	
All mammalian muscle	**300**	158	*Highest GEMS/Food cluster (sum of different species)*	158 (M)	428	*Highest value reported in different species above*	57	*Australia, 2–6 years (sum of different species)*	90	*Highest value reported in different species above*	—
Mammalian trimmed fat, skin and added fat	**50**	37	*Highest GEMS/Food cluster, higher than Czech Republic, adults (21)*	37 (K)	53.1	*USA, 97.5th percentile consumers only, 2 days, unique survey with this category and more than 1 day*	9	*USA, 2–6 years*	30	*USA, 97.5th percentile consumers only, 2 days, unique survey with this category and more than 1 day*	—
Mammalian offal											
Mammalian liver	**100**	4	*Highest GEMS/Food cluster*	4 (B; cattle)	250	*USA, 97.5th percentile, 2 days*	0.04	*USA, based on 2 consumers, 2–6 years*	—	*No chronic consumption reported in any country*	—
Mammalian kidney	**50**	4	*Highest GEMS/Food cluster*	4 (B; cattle)	200	*USA, 97.5th percentile, 2 days*	0.05	*Australia, based on 3 consumers, 2–6 years*	—	*No chronic consumption reported in any country*	—
Mammalian lung		—	*No chronic consumption reported in any country*	—	—	*No chronic consumption reported in any country*	—	*No chronic consumption reported in any country*	—	*No chronic consumption reported in any country*	—
All mammalian offal		14	*Highest GEMS/Food cluster, higher than Brazil, >2 years (12)*	14 (B)	250	*Highest value observed in the different organs*	2	*Czech Republic, 4–9 years*	109	*Czech Republic, 4–9 years, 2 days, 97.5th percentile*	—

Food type as raw commodity	Current JECFA model diet for veterinary drug residues (g/person per day)	General population[a]					Children[b]				Infants[c]
		Mean total population (g/person per day)	*Comments*	Mean total population (highest GEMS/Food cluster) (g/person per day)	High-level chronic consumers (g/person per day)	*Comments*	Mean total population (g/person per day)	*Comments*	High-level chronic consumers (g/person per day)	*Comments*	(g/person per day)
								(edible offal, farmed animals)		*consumers only, includes poultry offal*	
Fish and seafood											
Fish		57	*Spain, 17–60 years*	34 (F)	1000	*Brazil, 97.5th percentile, 2 days, unpublished data*	31	*Spain, 3–9 years*	175	*Spain, 3–9 years, 97.5th percentile consumers only*	—
Crustaceans		5	*Highest GEMS/Food cluster*	5 (M)	376	*Brazil, 97.5th percentile, 2 days, unpublished data*	2	*Italy, 3–9 years*	124	*Netherlands, 97.5th percentile consumers only, 2–6 years, 3 days*	—
Molluscs		15	*Highest GEMS/Food cluster, higher than Spain (12), 17–60 years*	15 (G)	325	*Germany, 97.5th percentile consumers only, 2 days*	9	*Italy, 3–9 years*	216	*Italy, 3–9 years, 97.5th percentile consumers only, 3 days, 37 consumers*	—
All fish and seafood	**300**	80	*Japan*	71 (L)	237	*Spain, 97.5th percentile consumers only, 2 days*	40	*Italy, 3–9 years; 36 Japan, 1–6 years*	181	*Italy, 3–9 years, 97.5th percentile consumers only, 3 days*	—
Poultry muscle	**300**	131	*Highest GEMS/Food cluster, higher than individual surveys; Australia 164, but 1-day survey only*	131 (K)	300	*Brazil, 97.5th percentile, 2 days, unpublished data*	37	*Spain, 3–9 years; 32 Hungary, 3–5 years*	207	*Czech Republic, 97.5th percentile consumers only, 2 days*	—
Poultry fat and skin	**50**	37	*No data available; copied from mammalian*	21 (H)	43	*No data available; copied from GEMS/Food large portion diet (USA)*	9	*No data available; copied from mammalian fat*	15	*No data available; copied from GEMS/Food large portion diet (USA)*	—

Food type as raw commodity	Current JECFA model diet for veterinary drug residues (g/person per day)	General population[a]					Children[b]				Infants[c]
		Mean total population (g/person per day)	*Comments*	Mean total population (highest GEMS/Food cluster) (g/person per day)	High-level chronic consumers (g/person per day)	*Comments*	Mean total population (g/person per day)	*Comments*	High-level chronic consumers (g/person per day)	*Comments*	(g/person per day)
Poultry offal	**100 + 50**	10	*Hungary, 3 days, consumers only, >18 years*	2 (I)	188	*Brazil, 97.5th percentile, 2 days, unpublished data*	2	*Czech Republic, 4–9 years, includes mammalian offal*	109	*Czech Republic, 4–9 years , 2 days, 97.5th percentile consumers only, includes mammalian offal*	—
Eggs (all)	**100**	71	*Highest GEMS/Food cluster, higher than individual surveys*	71 (H)	150	*Brazil, 97.5th percentile, 2 days, unpublished data*	28	*Japan, 1–6 years*	115	*Italy, 3–9 years, 97.5th percentile consumers only, 3 days*	—
Milk[d]	**1500**	378	*Spain; Australia 758, but 1-day survey only*	302 (G)	1057	*Denmark, 97.5th percentile consumers only, 7 days*	634	*Australia, 2–6 years, 2 days*	1065	*USA, 97.5th percentile consumers only, 2–6 years, 2 days*	750
Honey	**50**	2.5	*Germany*	2 (B)	140	*Belgium, 2 days, consumers only, 72 consumers; second highest: 74, Hungary, 3 days, consumers only, >18 years, 155 consumers*	2	*Czech Republic, 4–9 years*	84	*Spain, 3–9 years, 97.5th percentile consumers only, 2 days*	—

[a] The values provided are assumed to apply to the general population aged 2 years and over; however, some of the data sets submitted did not cover this specific age range (see Annex 3 for details).
[b] Children 2–6 years of age.
[c] Infants 0–3 months of age.
[d] Includes whole liquid milk, secondary milk products (e.g. skimmed milk, evaporated milk, milk powders), derived milk products (e.g. cream, butter) and manufactured milk products (yoghurt, cheese, ice cream).

muscle but higher than chronic high consumption of sheep and other ovines (146 g), goat and other caprines (169 g) and poultry (244 g).

As the highest data point from any country was taken to represent the food consumption amount for each food, the Expert Meeting emphasized that the proposed chronic dietary exposure model is a constructed diet and is not intended to represent the diet of any specific population. Rather, it is intended to make a conservative estimate of chronic dietary exposure that takes into account the non-average person who may be a high consumer of a single food.

5. Worked examples

The proposed chronic dietary exposure model was applied to two worked examples, as summarized in sections 5.1 and 5.2 below. In addition, for comparative purposes, the chronic exposures for the two chemicals used in these worked examples were recalculated using the existing JMPR approach for estimating chronic dietary exposure to pesticide residues (section 5.3). Finally, GECDE values for the antimicrobial colistin have been derived for the general population aged 2 years and over, children 2–6 years of age and infants, for comparison with estimates of TMDI and EDI values provided previously in this report (section 5.4).

5.1 Triclabendazole

The proposed chronic dietary exposure model was applied to the anthelminthic triclabendazole based on median residue concentrations from the depletion curve at the 28th day after treatment for cattle and sheep. These were corrected by the marker/total ratio for each commodity and bioavailability of 13%. The GECDE was calculated by first assessing high chronic exposure for all foods individually, and second by determining which food gave the highest estimated exposure value. In this case, cattle liver gave the highest value. This high value was then added to the sum of mean chronic dietary exposures for the general population for all other foods (highlighted values) to give a GECDE of 83 µg/person per day (Table 5). It is noted that as food consumption data were available for "all kidney", "all liver" and "all fat" only and not by individual animal species, the same consumption data were used for cattle and sheep tissues to determine which species was likely to result in the higher

Table 5. GECDE calculation for triclabendazole for cattle and sheep (general population)

Food categories	Median residue concentration from regression line (µg/kg)	Corrected residue concentration (µg/kg)[a]	Food consumption, high chronic (g/day)	Food consumption, mean chronic (g/day)	High chronic exposure (µg/person per day)	Mean chronic exposure (µg/person per day)
Cattle muscle	160.6	65.3	325	127	21.2	**8.3**
Cattle kidney	172.5	93.5	200	4	18.7	**0.4**
Cattle liver	423.1	289.5	250	4	**72.4**	1.2
Cattle fat	100.0	32.5	53	37	2.3	**1.2**
Sheep muscle	103.4	33.6	373	11	12.5	**0.4**
Sheep kidney	93.3	50.5	200	4	10.1	0.2
Sheep liver	154.1	80.1	250	4	20.0	0.3
Sheep fat	100.0	32.5	70	37	2.3	1.2
GECDE						**82.7**[b]

[a] The correction includes the ratio of marker residue concentration to total residue concentration for each tissue and the factor for bioavailability. Total residue = marker residue/ratio (marker/total) × bioavailability. Ratios of 0.32, 0.24, 0.14 and 0.4 for cattle muscle, kidney, liver and fat and of 0.4, 0.24, 0.25 and 0.4 for sheep muscle, kidney, liver and fat. Bioavailability of 13%.

[b] The GECDE is the sum of the highlighted values for high chronic exposure and mean chronic exposure.

dietary exposure. In this case, it was cattle liver, cattle kidney and cattle fat. To avoid double-counting the amount of offal consumed, the values for sheep for these organs were not included in the total estimate. The main contributor to the estimated chronic dietary exposure to triclabendazole was cattle liver.

Dietary exposure values can be calculated for both the general population and children. Table 5 shows the results for the general population; results for children are not given here, as children have lower consumption of offal (see Table 4).

5.2 Monepantel

The proposed chronic dietary exposure model was applied to the anthelminthic monepantel based on residue concentrations from the depletion curve at the 28th day after treatment for sheep, using the approach detailed above; however, this calculation was straightforward, as only one animal species was included. The GECDE was calculated to be 275 µg/person per day (Table 6) using the high exposure value for sheep liver and the mean exposures for all other foods. The main contributor to the estimated chronic dietary exposure was sheep liver.

Table 6. GECDE for monepantel for sheep (general population)

Food categories	Median residue concentration from regression line (µg/kg)	Corrected residue concentration (µg/kg)[a]	Food consumption, high chronic (g/day)	Food consumption, mean chronic (g/day)	High chronic exposure (µg/person per day)	Mean chronic exposure (µg/person per day)
Sheep muscle	76.0	71.4	373	11	26.6	**0.8**
Sheep kidney	169.0	240.7	200	4	48.1	**1.0**
Sheep liver	595.0	847.4	250	4	**211.9**	3.4
Sheep fat	1156	1646.4	70	37	115.3	**60.9**
GECDE						**274.6**[b]

[a] The correction includes the ratio of marker residue concentration to total residue concentration for each tissue and the molecular weight correction. Total residue = marker residue/ratio (marker/total) × molecular weight correction. Ratios of 1.0 for muscle and 0.66 for kidney, liver and fat. Molecular weight correction of 0.94.

[b] The GECDE is the sum of the highlighted values for high chronic exposure and mean chronic exposure.

Dietary exposure values can be calculated for both the general population and children. Table 6 shows the results for the general population; results for children are not given here, as children have lower consumption of offal (see Table 4).

5.3 Comparison of the approach for chronic dietary exposure assessment used by JMPR with the current and proposed JECFA models

For comparison with the existing JMPR approach for estimating chronic dietary exposure to pesticide residues, the chronic exposures for the two chemicals used in the examples above were recalculated using the JMPR method. Chronic dietary exposure assessments for pesticide residues in food commodities, including those from animal origin (arising from the use of pesticides on foodstuffs used as feed), are conducted by JMPR for each pesticide residue by multiplying the concentration of residues (STMR concentration found in the studies) by the average daily per capita consumption for each commodity from the 13 GEMS/Food consumption cluster diets (http://www.who.int/foodsafety/chem/gems/en/index1.html). The

international estimated daily intake (IEDI) for a compound in each cluster diet is the sum of the per capita dietary exposure from the consumption of all commodities for each diet.

Table 7 shows the chronic dietary exposure assessments for monepantel (evaluated at the seventy-fifth meeting of JECFA) and triclabendazole (evaluated at the seventieth and seventy-fifth meetings of JECFA) calculated using the current model diet (EDI), the proposed model diet (GECDE) and the cluster diet approach (IEDI) for one withdrawal period (days after treatment). The Expert Meeting did not receive adequate consumption data to develop a model that could report specific values for sheep fat, liver and kidney. Therefore, in this case, the larger categories, mammalian fat, mammalian liver and mammalian kidney, were used in the estimation of the GECDE. This is likely to lead to an overestimation of the exposure for monepantel, which is used only in sheep. The IEDI approach aims to reflect the average long-term exposure of the total population to a residue from a wide range of food commodities and is not expected to reflect the long-term exposure of habitual consumers of specific commodities. The predicted dietary exposure using the IEDI approach tends to be lower in value than that predicted using the EDI and GECDE approaches.

Table 7. Comparison of chronic dietary exposure assessments for monepantel and triclabendazole

Food categories	Median total residue (µg/kg)	Dietary exposure (µg/person per day)		
		Current model diet (EDI)	Proposed model[a] (GECDE)	Cluster diet[b,c] (IEDI)
Monepantel[d] (13 days after treatment)				
Sheep muscle	71	191.7	274.6	5.9 (cluster B)
Sheep kidney	241			
Sheep liver	847			
Sheep fat, subcutaneous	1646			
Triclabendazole[e] (28 days after treatment)				
Cattle muscle	65.2	54.8	82.7	8.9 (cluster M)
Cattle kidney	93.4	(cattle only)		
Cattle liver	289.5			
Cattle fat	32.5			
Sheep muscle	33.6	22.2		
Sheep kidney	50.5	(sheep only)		
Sheep liver	80.1			
Sheep fat	32.5			

[a] Consumption data on mammalian fat, kidney and liver, cattle and sheep muscle (see Tables 5 and 6).
[b] IEDI for the cluster diet with the highest value.
[c] The GEMS/Food consumption cluster diet does not include consumption data for sheep liver and kidney.
[d] Total residue = maker residue/ratio (marker/total) × molecular weight correction. Ratios of 1.0 for muscle and 0.66 for kidney, liver and fat. Molecular weight correction of 0.94.
[e] Total residue = marker residue/ratio (marker/total) × bioavailability. Ratios of 0.32, 0.24, 0.14 and 0.4 for cattle muscle, kidney, liver and fat and of 0.4, 0.24, 0.25 and 0.4 for sheep muscle, kidney, liver and fat. Bioavailability of 13%.

5.4 Illustration of the proposed approach for chronic dietary exposure assessments using the example of colistin[1]

Estimates of TMDI and EDI values for the antimicrobial colistin, based on the residues monograph considered by the sixty-sixth meeting of JECFA in 2006 (FAO/WHO, 2006b), are provided in Tables 1 and 2 of this report. For comparison, the same data have been used to derive GECDE values for the general population, children and infants.

Residues of colistin reported in the residues monograph were below the LOQ for the method of analysis in most tissues of most species. Low but quantifiable residues were detected in the fat of orally treated rabbits and in eggs of laying hens treated by intramuscular injection. Quantifiable residues of colistin were also found in cows' milk following intramammary infusion and intramuscular injection. As a consequence, the highest residue values reported in Table 2 also represent the only residue values that need to be taken into consideration in the GECDE assessments. This allows for direct comparison between the EDI and GECDE.

The ADI for colistin is 0–7 µg/kg bw. The TMDI value for colistin, based on MRL values, was 229 µg/person per day (3.8 µg/kg body weight per day for a 60 kg adult). Using median residue values, the EDI value was 56.9 µg/person per day (1.0 µg/kg body weight per day for a 60 kg adult). The GECDE values for adults, children and infants are 53.8 µg/person per day (0.9 µg/kg body weight per day for a 60 kg adult), 18.2 µg/person per day (1.2 µg/kg body weight per day for a 15 kg child) and 10.3 µg/person per day (2.1 µg/kg body weight per day for a 5 kg infant) (Tables 8 and 9).

Table 8. Assessment of GECDE for colistin for the general population

Food type as raw commodity (including food consumed processed)	Food consumption (g/day)		Median residue (µg/kg)[a]	Exposure from each food (µg/day)	
	Mean chronic	High chronic		High consumers	Mean total population
Mammalian muscle					
Beef and other bovines	127	325			
Pork and other porcines	69	428			
Sheep and other ovines	11	373			
Goat and other caprines	5	401			
Horse and other equines	2				
Rabbit	5				
All mammalian muscle	158	428			
Mammalian trimmed fat, skin and added fat	37	70	82		**3.8**
Mammalian offal					
Mammalian liver	4	250	38		**0.2**
Mammalian kidney	4	200	145	**36.3**	
Mammalian lung					
All mammalian offal	14	250			

[1] It should be noted that this example was selected because data were available from a recent JECFA evaluation, even though the ADI for colistin was based on an acute end-point. The goal of the exercise was to compare the outcomes of different approaches to estimating dietary exposure with the ADI, not to discuss the hazard characterization.

Food type as raw commodity (including food consumed processed)	Food consumption (g/day)		Median residue (µg/kg)[a]	Exposure from each food (µg/day)	
	Mean chronic	High chronic		High consumers	Mean total population
Fish and seafood					
Fish	57	1000			
Crustaceans	5	376			
Molluscs	15	325			
All fish and seafood	80	237			
Poultry muscle	131	300	38	**14.3**	**6.2**
Poultry fat and skin	37	43			
Poultry offal	10	188			
Eggs (all)	71	150	24	**4.5**	**2.1**
Milk	378	1057	11	**14.5**	**5.2**
Honey	2.5	140			

Mean exposure from all foods	**18.3**	µg/day per person
Mean exposure for adult of 60 kg body weight	**0.3**	µg/kg body weight per day
GECDE	**53.8**	µg/day per person
GECDE for adult of 60 kg body weight	**0.9**	µg/kg body weight per day

[a] The colistin residues were measured by a microbiological method that does not report all analytes. As the marker residue colistin A + B represents approximately 80% of the microbiologically active residues, the marker/total ratio of 0.8 is incorporated into the calculation of dietary exposure estimates to ensure that they correctly reflect residues of microbiological concern.

Table 9. Assessment of GECDE for colistin for children and infants

(a) Children

Food type as raw commodity (including food consumed processed)	Food consumption (g/day)		Median residue (µg/kg)[a]	Exposure from each food (µg/day)	
	Mean chronic	High chronic		High consumers	Mean total population
Mammalian muscle					
Beef and other bovines	39	88			
Pork and other porcines	25	90			
Sheep and other ovines	13				
Goat and other caprines					
Horse and other equines					
Rabbit					
All mammalian muscle	57	90			
Mammalian trimmed fat, skin and added fat	9	30	82	3.1	**0.9**
Mammalian offal					
Mammalian liver	0.04		38		**0.0**
Mammalian kidney	0.05		145		**0.0**

Food type as raw commodity (including food consumed processed)	Food consumption (g/day)		Median residue (µg/kg)[a]	Exposure from each food (µg/day)	
	Mean chronic	High chronic		High consumers	Mean total population
Mammalian lung					
All mammalian offal	2	109			
Fish and seafood					
Fish	31	175			
Crustaceans	2	124			
Molluscs	9	216			
All fish and seafood	40	181			
Poultry muscle	37	207	38		**1.8**
Poultry fat and skin	9	15			
Poultry offal	2	109			
Eggs (all)	28	115	24		**0.8**
Milk	634	1065	11	**14.6**	
Honey	5	84			

Mean exposure from all foods	**12.2**	µg/day per person
Mean exposure for child of 15 kg body weight	**0.8**	µg/kg body weight per day
GECDE	**18.2**	µg/day per person
GECDE for child of 15 kg body weight	**1.2**	µg/kg body weight per day

(b) Infants

Food type as raw commodity (including food consumed processed)	Food consumption (g/day)	Median residue (µg/kg)[a]	Exposure from each food (µg/day)	
	Mean chronic		Mean total population	
Milk	750	11	**10.3**	µg/day

GECDE for infant of 5 kg body weight	**2.1**	µg/kg body weight per day

[a] The colistin residues were measured by a microbiological method that does not report all analytes. As the marker residue colistin A + B represents approximately 80% of the microbiologically active residues, the marker/total ratio of 0.8 is incorporated into the calculation of dietary exposure estimates to ensure that they correctly reflect residues of microbiological concern.

6. Limitations, assumptions and uncertainties in dietary exposure estimates for veterinary drug residues

The development of an exposure model is dependent on the availability of food consumption data and on the statistical methods available to evaluate them. It is also necessary to consider the appropriate residue data (median, high concentration or MRL) for use in dietary exposure calculations.

6.1 Food consumption data

Food consumption data available at the national level are gathered for many purposes, including nutritional and economic, but seldom for the purpose of the dietary exposure assessment of food chemicals. This means that the ways in which the data are collected, summarized and presented may not always be relevant to the categories of food for which veterinary drug residue data are available. Particular data limitations are briefly described below.

- *Level of food classification*

Depending on the purpose of the survey and the degree of aggregation of the reported results, information about consumption of specific categories of food may or may not be available. In particular, some surveys may record consumption of products from specific animal species such as beef, lamb and pork, whereas others may record "meat and meat products" only. This means that when selecting data for use in a dietary exposure assessment, either the highest level of food grouping must be selected, resulting in loss of specificity, or lower food classification levels are used, which may result in data gaps for some data sets.

Data for fat are not always available, and assumptions may need to be made about the proportion of meat product that is trimmable fat (e.g. 10% poultry or 20% meat). Consumption of dairy products (cream, cheese, butter, etc.) has been incorporated into the consumption figure for milk in some countries that express these products as whole milk equivalents, assuming set conversion factors. If consumption is not reported in this way, conversion factors would need to be applied to the amounts of processed dairy products consumed.

In general, there may be some difficulties in matching food consumption data to the definitions of the commodities used in veterinary drug residue evaluations (see Glossary).

- *Composite foods*

Food consumption surveys usually record amounts of food "as eaten", so that products derived from animal products (e.g. cheese or yoghurt) and composite foods that may include animal products as ingredients (e.g. sausages or casseroles) are recorded separately from direct consumption of meat offal, eggs or milk. In such cases, it is necessary to convert the consumption of animal products in processed foods and composite foods back to the raw animal product equivalent amount using "recipe" data. Some food consumption surveys do not distinguish between animal products in composite and processed foods and those consumed directly, which results in a further source of uncertainty in the models.

These consumption data need to be incorporated into the total consumption figure for each raw animal product included in the chronic exposure model.

- *Representation of high-level consumers*

There is variability in the amounts of animal products consumed by individuals that should be taken into account when considering both acute and chronic dietary exposures to food chemicals. Surveys that report per capita consumption only will underestimate consumption of food by consumers of that food, in particular by high-level consumers. Many sets of survey data do report high-level consumption, but the value provided may be a 90th, 95th, 97.5th or some other percentile. The maximum is seldom used, because it is considered statistically unreliable. In order to provide consistency, the 97.5th percentile value for consumers only of the food of interest has been chosen whenever available for use in dietary exposure estimates for veterinary drug residues. GEMS/Food compiles a large portion size database of 97.5th percentile food consumption amounts based on 1-day records that are suitable for use in acute dietary exposure estimates. In this case, if records are available for individuals participating in the survey for more than 1 day, each of their 1-day records is treated as a separate record, and the individual is counted as a consumer of the food of interest if he or she reported consuming that food on the day of the record.

The choice of the 97.5th percentile to represent high consumers of a single food in the chronic dietary exposure model was justified by its application for a single commodity (instead of two, as for other food chemicals), noting that in this case, this value should be derived from food consumption records reported in surveys of 2 or more days' duration by first calculating the average food consumption amount per day over the number of survey days. In this case, an individual is counted as a consumer of the food of interest if he or she reported consuming that food on 1 or more of the survey days.

Another reason was that the 97.5th percentile of food consumption was more commonly reported in the data submitted. However, the experts recognized that the 90th or 95th percentile can also be considered to represent chronic (regular) high consumption. It should be noted that for infrequently consumed foods, the number of consumers could be insufficient to calculate a reliable high percentile. In any case, it is essential to document information on the number of consumers on which the percentiles are based.

- *Duration of food consumption survey*

In general, for infrequently consumed foods in particular, as the duration of the survey increases, the number of consumers counted increases (a survey participant is counted as a consumer of the food of interest if he or she reported consumption on 1 or more days of the survey), but the average daily consumption amount decreases. It was noted that for very infrequently consumed foods, even the use of 2- to 7-day survey data might underestimate the true number of consumers and overestimate true consumption in the longer term.

If data on the amounts consumed (portion size) and frequency of consumption (days on which eaten) are available, then it may be possible to extrapolate the average consumption over any time period (Slob, 2006). Other statistical techniques may also be applied if the original raw population data are available (Carrington & Bolger, 2001). The subject of extrapolating dietary data to estimate "usual" food consumption amounts or dietary exposure has been reviewed by van der Voet & van Klaveren (2010), Kipnis et al. (2009), Zhang et al.

(2011) and Tooze et al. (2006, 2010). Unfortunately, most data made available to the Expert Meeting were summarized survey data, not allowing such extrapolations.

- *Age of subject*

The most common age banding for reporting consumption by children was found to be 2–6 years, and so this was adopted as a standard for the dietary exposure models. However, in order to make best use of available data, all children's data were considered, even if the age range reported did not fit exactly with the standard age category.

Very few food consumption data for infants were provided by contributing countries. As a consequence, a single figure approach, based on the WHO default assumptions for a 3-month-old infant of consumption of 0.75 litre of infant formula and a body weight of 5 kg (WHO, 2011), was proposed for use in both acute and chronic dietary exposure estimates.

- *Body weight correction*

For many surveys, food consumption data are not reported on a gram per kilogram body weight basis, calculated on an individual basis. However, these data may be available upon request to submitting countries. Using food consumption data expressed per kilogram body weight is the most accurate and preferred data set for use in generating dietary exposure estimates that are directly comparable with the relevant health-based guidance value, such as the ADI.

When data are reported only on a gram per day basis, they must be corrected using either a record of an individual's body weight or an average body weight for that age group. The former method is the preferred one. In the latter case, if the survey covers a wide range of ages, then the use of average body weight for the whole population may result in an over-estimation of dietary exposure in individuals with lower actual body weights and an under-estimation of dietary exposure in individuals with higher body weights. Average body weights by country are to be made available shortly on the WHO JECFA web site.

6.2 Residue data

It is anticipated that the MRL value could occur in food only where a food product consists entirely of an unprocessed tissue, such as a steak. For a food sourced from different animals that is mixed before entering the food-chain, it is assumed that the residue would be distributed throughout a batch of product and the residue concentration would not be higher than in the raw commodity. In such circumstances, the median residue concentration from depletion studies could be considered to represent the maximum concentration in the commodity offered for sale instead of using the maximum residue concentration from an individual sample analysed prior to the mixing process. This may apply to milk and to products that are mixed, but should be assessed on a case-by-case basis. However, for evaluations at an international level, it was considered that the high residue concentration should be selected for all commodities for use in acute dietary exposure estimates, because some countries do not produce food in this way. As these details are often unknown, this represents a source of uncertainty in the data.

The chronic dietary exposure model relates to long-term exposure. In accordance with the conclusions of the sixty-sixth meeting of JECFA (FAO/WHO, 2006b), the median value or

the upper limit of the 95% confidence interval of the median from depletion studies should be used in exposure estimates, because consumers are unlikely to be repeatedly exposed to tissues containing the MRL in the longer term. It was noted that in the absence of reliable occurrence data, it must be assumed that all foods in an individual's diet contain the residue of concern at the median concentration and at all times. In reality, only a proportion of the supply of animal products in the food-chain will contain residues of veterinary products, and so this represents a conservative assumption.

6.3 Modelling methods

Modelling uncertainties relate to the statistical methods available for summarizing and managing data. Ideally, the original individual daily food consumption records from dietary surveys would be available in a database that could be interrogated to answer specific questions. The reality is that often only summary data (population means, percentiles, etc.) are available at an international level, and so methods are required that generate the best representation of the likely results of more realistic exposure models.

In this proposed approach for chronic dietary exposure assessment, the highest reported mean consumption values were selected for different animal species from countries contributing data. Therefore, the addition of mean consumption amounts for animal species for a total consumption amount for each commodity is likely to result in a higher total value than would be found in any one country (e.g. adding beef, pork, ovine and other muscle consumption to create a total mammalian muscle consumption figure).

6.4 Uncertainty analysis

The International Programme on Chemical Safety (IPCS) Harmonization Project, *Guidance document on characterizing and communicating uncertainty in exposure assessment*, which was published in December 2008, recommends a tiered approach to the evaluation of uncertainties in exposure assessment (IPCS, 2008). This could be applied to estimation of acute and chronic exposures to veterinary drug residues in food. A simple qualitative uncertainty table is recommended in EFSA guidelines to provide methods for addressing uncertainties in dietary exposure assessment (EFSA, 2006).

7. Discussion, conclusions and recommendations for further development

7.1 Discussion and conclusions

The Expert Meeting reviewed the current model diet in the light of data submitted on mean total consumption for different population groups and noted that for some food commodities in some countries, actual food consumption data at the 97.5th percentile (one person-day data or averaged over survey duration) were higher per person per day than those used in the current model diet to represent a high level of consumption. In some cases, the current model diet may not be as conservative as previously assumed.

The experts noted that a model cannot be both simple and accurate and that simplifying the model may lead to higher exposure estimates.[1] From the data available, the Expert Meeting concluded that it was not helpful to simplify the current model diet, as it would not result in an improvement in the accuracy of either acute or chronic dietary exposure assessments. Rather, to enable a more accurate dietary exposure estimate, the list of foods in the new approach was expanded to incorporate available food consumption data for different animal species where sufficient data were available. This expansion of the list of foods was considered to be an improvement on the previous simplified model. Moreover, the experts' analysis of the simplified model showed that replacing the default food consumption estimates with actual food consumption figures failed to demonstrate the predicted decrease in modelled estimates of dietary exposure to veterinary drug residues.

A template of food commodities was developed that could be used in assessments of both acute and chronic dietary exposure to veterinary drug residues. For acute dietary exposure assessments, each food is evaluated singly, and for chronic dietary exposure assessments, all foods for which residue data are available are included in the constructed model diet. Food consumption amounts were derived for the general population aged 2 years and over, for the subpopulation of children aged 2–6 years and for infants (milk only), for mean and high consumers of each food.

Worked examples were completed using information available at the seventy-fifth meeting of JECFA to illustrate the proposed new approach to determining chronic dietary exposure estimates. A comparison with the current JMPR approach for chronic dietary exposure assessments was also made, noting that the proposed approach for JECFA aims to take a habitual high consumer of a single food into account, whereas that for JMPR is an estimate for the average population. This difference can be explained by the larger number of food commodities generally under consideration for pesticide residues and was noted by the JMPR Secretariat to be the subject of further discussions within JMPR.

The Expert Meeting noted that the currently available data did not support the development of a constructed model diet for different regions of the world.

[1] A simplified model for chronic dietary exposure estimation was submitted by Canada when the draft of this report was posted for public comment (see Annex 7). The experts recognized its validity and noted that it would lead to slightly higher exposure estimates.

The development of newer dietary exposure models for veterinary drug residues requires the incorporation of both new data and updated approaches to dietary exposure assessment. Food consumption database managers in approximately 50 Member countries have provided significant amounts of data, but the presentation of many of the data is inconsistent in terms of the level of description of food categories, the methods of data collection, handling of raw versus processed products and the provision of individual body weight–corrected data. This means that a further round of data collection will be required, and it is hoped that this will bring in data from additional countries.

A consequence of this inconsistency is that the data currently provided in the acute and chronic dietary exposure models must be considered provisional until the final data sets have been audited and the modelling methods validated.

The development of a new dietary exposure modelling approach for veterinary drug residues that was simple to use and yet provided conservative estimates of both acute and chronic dietary exposure, while reflecting national differences in food consumption patterns, presented a considerable challenge. Therefore, the proposed approaches will need careful evaluation before being adopted for routine use.

7.2 Recommendations for further development

Recommendations for further work to enable the evaluation of the approaches for acute and chronic dietary exposure assessment for veterinary drug residues proposed in this report are listed below.

7.2.1 Data requirements

This description of a proposed new approach to estimating dietary exposures to veterinary drug residues is based on information made available by Member countries responding to a call for data in 2010. At that time, it was not possible to provide a detailed specification for the information required. Now that a proposed model structure is available, there is an opportunity to improve the model by expanding the scope of and level of detail in the food consumption data.

- *National data*

There are currently insufficient data from different world regions to support a regional diet approach. Additional information from more countries spread across global regions would allow a more representative model diet. With more national data available, the potential for a regional diet approach could be explored in the future.

- *Level of food classification*

Some countries have been able to provide data on food consumption described at the animal species level, such as beef, pig or sheep liver. For other countries, only composite data, such as “mammalian liver” or “liver and offal”, are available. This issue particularly affects European countries, where EFSA’s Comprehensive Food Consumption Database does not provide species-categorized data. More species-specific data would improve precision in both acute and chronic models by better linking the models to actual residue concentrations in the tissues in which they may occur.

- *Individual body weight correction*

Within the general population and for children aged 2–6 years, there is a wide range of body weights. Therefore, dividing food consumption data presented on a gram per day basis by population-average body weights rather than individual body weights introduces uncertainty. Many countries have already provided food consumption data on a gram per kilogram body weight per day basis, where each individual in the survey has had his or her food consumption corrected for his or her individual body weight. Obtaining more individual body weight–corrected data would allow an increase in the accuracy of the acute and chronic dietary exposure assessment methods.

- *Food consumption data age ranges*

Food consumption surveys may contain data on varying age ranges depending on the purpose of the survey. For the acute and chronic veterinary drug residue exposure models, the key groups have been identified as the general population (i.e. all potential consumers of solid foods aged 2 years and over), children between the ages of 2 and 6 years and infants 0–3 months of age (consuming entirely milk or formulated products). The precision of the exposure models would be improved if database managers could provide data that correspond better to these age categories.

- *Less frequently consumed foods*

Tissues such as liver and kidney or minor species such as rabbit or quail, which can be consumed in significant portions on eating occasions, may be consumed relatively infrequently. There are also other tissue types (e.g. lung, intestine, heart) and species (e.g. horse and some fish species that may be farmed) for which limited or no data are available from individual surveys.

Basing food consumption estimates on surveys of only a few days' duration may result in a significant underestimation of the proportion of consumers consuming that food (or miss them entirely), while significantly overestimating average daily consumption in the longer term for those who do report consumption. Moreover, the limited number of eating days during the survey makes it difficult to assess high percentiles of both acute and chronic consumption for infrequently consumed foods. Improved estimates of true long-term consumption of such foods can be derived by combining portion sizes with food frequency data. Obtaining national information about portion sizes and frequency of consumption of certain tissues and minor species would improve the accuracy of the acute and chronic dietary exposure estimates. In the absence of such data, the consumption value for the more generic food category should be used (e.g. all mammalian offal), with various high percentiles, such as the 90th, 95th and 97.5th, reported with the corresponding number of consumers and number of days of survey duration on which they were based. Such an approach would cover the substitution between food items from the same category occurring over the long term for a high consumer of offal, but may overestimate the exposure of the high consumer of a single specific food item within the food category.

- *Composite foods*

Individual food consumption surveys are often conducted at the level of foods "as eaten" so that meat pies, soups, cakes and pastries are recorded separately from meat and other specific

animal products. As a consequence, it is necessary to estimate the meat, milk and egg content from composite foods in order to provide total consumption for the exposure model. Many data providers have national "recipe databases" that enable composite foods to be subdivided into their constituent parts. Obtaining food consumption data broken into their constituent animal product components would improve the precision of the acute and chronic dietary exposure assessment models.

- *Data audit and verification*

Before the models can be applied in veterinary drug residue risk assessments, it is necessary to ensure that the data contained in them are reliable. This can be undertaken in three steps:

1) Check all values in the dietary exposure models against the original values provided by national database managers.
2) Confirm with national database managers the nature of the data provided (survey days over which averaged, whether individual body weight applied, etc.) and seek confirmation that values used to represent total consumption (raw plus processed products) for each category reflect the database managers' understanding of the data.
3) Before finalizing the food consumption databases, FAO/WHO should consider a policy to manage data sets where there are too few data points to make reliable estimates of high-percentile food consumption. If necessary, high-percentile consumption estimates based on too few data points may be removed.

7.2.2 Approaches for dietary exposure assessment

The methods proposed for estimating acute and chronic dietary exposures to veterinary drug residues reflect a compromise between complex computer-based models utilizing raw individual data from food consumption surveys and simple, practical tools for making quick, conservative estimates. They are based on current practice in other sectors, such as food additives and pesticide residues, even if the methods are not strictly similar, and are intended to provide statistically robust approaches that make optimal use of the available data. However, there will always be scope for further development, and in particular some of the underlying assumptions warrant further consideration. There is also a need to better understand how the methods relate to actual consumer exposures so that the degree of conservatism (assuming this is present) can be assessed and, if possible, quantified.

- *Taking consumers of foods into account*

For veterinary drug residues with acute toxicity, the dietary exposure is calculated for a single food, taking a high level (97.5th percentile) of consumption of each of the foods nominated to contain the veterinary drug residue over one meal or 24 hours for consumers of that food only.

Normally, for a single data set, it is considered valid to add mean exposures from different foods together to get a total mean chronic dietary exposure for the total population (i.e. consumers and non-consumers), but it is not considered valid to sum the exposure for consumers only of each food to derive a total chronic dietary exposure, as the consumers are drawn from different subpopulations, and the total amount of food assumed to be consumed would be unrealistically high.

The chronic model is a constructed model diet that aims to take account of people who consistently consume one food or food group at a high level over a long period of time. It is based on estimates of mean consumption for all individuals in a population and high-level consumption by consumers only of one food, that one food being selected from all those nominated to contain the veterinary drug residue, because it is likely to give rise to the highest dietary exposure for a high consumer of the food. This is done because the comparative exercise on national-level data (see Annex 4) indicates that, in most cases, a constructed model such as the one proposed gives a similar answer to one based on the same data set but using a calculated high percentile of dietary exposure from distributional data for individuals.

Obviously, if distributional data are available at a national level, it would be preferable to use the full data set to determine high percentiles of dietary exposure to veterinary drug residues, not the proposed model. At an international level, however, this model is proposed as a "proxy", as individual data are not available for use for all regions in the world by committees such as JECFA. However, this approach may introduce some uncertainty into the method, and so its consequences require further investigation (see section on uncertainty analysis below).

- *Veterinary drugs with other uses or occurrence*

Certain substances used in veterinary medicines may also be used in other product types, such as pesticides, or may occur in natural products or as contaminants (e.g. in drinking-water). The acute and chronic exposure models require expansion and modification so that such simultaneous occurrence can be incorporated into the models.

- *Background exposure in acute exposure modelling*

The acute exposure model makes the assumption that the distribution of occurrence of veterinary residues in food is such that it is unlikely that a consumer will be exposed from more than one significant source during an acute exposure episode. However, there may be other residues present, or there may be background uptake resulting from previous long-term exposure. The possible effect of background exposure on estimates of acute exposure requires further investigation.

- *Uncertainty analysis and conservatism*

All of the input variables and the model itself are subject to uncertainty. The current report includes an initial evaluation of uncertainty as recommended in IPCS (2008) guidelines. However, the quantitative impact of uncertainties within the data and methods and their impact on results require further consideration. This will allow the degree of conservatism associated with the method to be assessed and quantified. In particular, estimation of actual exposure based on monitoring data for veterinary drugs should be useful to quantify the degree of conservatism of median residue values for long-term exposure assessment. The Expert Meeting noted that monitoring data are likely to be available only at a national level and that for many veterinary drugs, the MRL is set at or near the limit of reporting.

- *Development of worked examples*

Additional worked examples will provide a means of identifying the strengths and weaknesses of the proposed approaches.

- *Testing and evaluation*

The proposed approaches for acute and chronic dietary exposure assessment have been compared with results that would be obtained using the current model diet approach in a limited number of cases. Further comparisons are required to investigate the full utility of the new methods and identify areas where further refinements may be required. There is also a need to evaluate the approaches against results that would be obtained using individual data from food consumption surveys at a national level.

As stated in the Introduction, the purpose of this report is not to describe the process for deriving MRLs for veterinary drugs. However, if adopted by JECFA, the approaches described in this report would be used in estimating dietary exposures to veterinary drug residues. Consideration should be given to the potential impact that this would have on the MRLs that can be recommended.

- *Need for periodic review*

Food consumption patterns change, and food consumption surveys are constantly being renewed. This means that revised estimates of the amounts of food consumed for the food categories considered can be anticipated in the future. However, given the conservatism associated with the current approach, any such revised food consumption estimates may not be meaningful in terms of the results. Thus, any updates of food consumption data should be evaluated within the context of the uncertainty analysis and the models revised only if the change is likely to be meaningful.

Periodic review will be necessary to take account of cumulative changes in food consumption data and developments in the science of exposure analysis. Therefore, it is recommended that a review of the methods be undertaken on a regular basis, and no less than every 10 years.

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Glossary[1]

Acceptable daily intake (ADI): An estimate by the Joint FAO/WHO Expert Committee on Food Additives of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk.

Acute reference dose (ARfD)*: The estimate of the amount of a substance in food or drinking-water, expressed on a body weight basis, that can be ingested in a period of 24 hours or less without appreciable health risk to the consumer. It is derived on the basis of all the known facts at the time of evaluation. The ARfD is expressed in milligrams of the chemical per kilogram of body weight.

Edible offal: Historically considered by the Joint FAO/WHO Expert Committee on Food Additives to include only liver and kidney. For the purposes of this report, the definition of edible offal has been expanded to include lung.

Egg: The fresh edible portion of the spheroid body produced by female birds, especially domestic fowl. *Portion of the commodity to which the maximum residue limit applies*: The edible portion of the egg including the yolk and egg white after removal of the shell.

Estimated daily intake (EDI):** An estimate of dietary exposure to residues of veterinary drugs for use in the evaluation of chronic toxicity and chronic dietary exposure based on a specific model diet and median residue concentrations, adjusted for marker total. In calculating the median from an array of results including values below the limit of quantification or below the limit of detection, half of the respective limit is used for the calculation of median concentrations of residues.

Fat: The lipid-based tissue that is trimmable from an animal carcass or cuts from an animal carcass. It may include subcutaneous, omental or perirenal fat. It does not include interstitial or intramuscular carcass fat or milk fat. *Portion of the commodity to which the maximum residue limit (MRL) applies*: The whole commodity. For fat-soluble compounds, the fat is analysed, and MRLs apply to the fat. For those compounds where the trimmable fat is insufficient to provide a suitable test sample, the whole commodity (muscle and fat but without bone) is analysed, and the MRL applies to the whole commodity (e.g. rabbit meat).

Fish: Any of the cold-blooded aquatic vertebrate animals commonly known as such. This includes Pisces, Elasmobranchs and Cyclostomes. Aquatic mammals, invertebrate animals and amphibians are not included. It should be noted, however, that this term may also apply to certain invertebrates, particularly Cephalopods.

Food balance sheet*: Gross estimates of national per capita availability of food commodities derived from a country's annual food production plus imports minus exports. Food waste, refuse, losses from spoilage and other sources of waste are not taken into account.

[1] Definitions have been taken directly or with slight modification from the *Codex glossary of terms and definitions (residues of veterinary drugs in foods)*, CAC/MISC 5-1993, amended 2003 (not marked with an asterisk); EHC 240 (FAO/WHO, 2009c) (marked with an asterisk); or FAO/WHO (2006b) (marked with a double asterisk).

GEMS/Food consumption cluster diets*: Per capita consumption of raw and semiprocessed agricultural commodities expressed in grams per person per day for distinct groups of the world's population that share similar dietary patterns. Based on FAO food balance sheet data, the diets were generated using a cluster analysis, which assigned countries to one of the 13 cluster diets.

Health-based guidance value*: A numerical value derived by dividing a point of departure (a no-observed-adverse-effect level, benchmark dose or benchmark dose lower confidence limit) by a composite uncertainty factor to determine a concentration that can be ingested over a defined time period (e.g. lifetime or 24 hours) without appreciable health risk.

International estimated daily intake (IEDI)*: A prediction of the long-term daily intake of a pesticide residue on the basis of the assumptions of average daily food consumption per person and median residues from supervised trials, allowing for residues in the edible portion of a commodity and including residue components defined by the Joint FAO/WHO Meeting on Pesticide Residues for estimation of dietary intake. Changes in residue concentrations resulting from preparation, cooking or commercial processing are included. When information is available, dietary intake of residues resulting from other sources should be included. The IEDI is expressed in milligrams of residue per person.

Large portion size*: A food consumption amount that represents the 97.5th percentile consumption (eaters only) of a food that is derived from individual consumer days in a food consumption survey. This is useful in calculating acute dietary exposures.

Limit of detection (LOD)*: The minimum concentration of a component in a dietary sample that can be qualitatively detected, but cannot be quantitatively determined, under a pre-established set of analytical conditions.

Limit of quantification (LOQ)*: The minimum concentration of a component that can be determined quantitatively with acceptable accuracy and consistency. It often approximates to a value of 3 times the limit of detection.

Margin of exposure*: Ratio of the no-observed-adverse-effect level or benchmark dose lower confidence limit for the critical effect to the theoretical, predicted or estimated exposure dose or concentration.

Marker residue: A residue whose concentration decreases in a known relationship to the level of total residues in tissues, eggs, milk or other animal tissues. A specific quantitative analytical method for measuring the concentration of the residue with the required sensitivity must be available.

Marker/total ratio: The ratio between the concentration of the marker residue in a tissue or commodity and the concentration of the total residue expressed as equivalents of parent drug.

Maximum residue limit (for veterinary drugs) (MRL): The maximum concentration of residue resulting from the use of a veterinary drug (expressed in milligrams per kilogram or micrograms per kilogram on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food. It is based on the type and amount of residue considered to be without toxicological hazard for human health as expressed by the acceptable daily intake (ADI) or on the basis of a

temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects. When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available.

The MRLs elaborated by the Joint FAO/WHO Expert Committee on Food Additives are "recommended MRLs" that are forwarded to the Codex Committee on Residues of Veterinary Drugs in Foods for consideration.

Meat: The edible part of any mammal.

Milk: The normal mammary secretion of milking animals obtained from one or more milkings without either addition to it or extraction from it, intended for consumption as liquid milk or for further processing. *Portion of the commodity to which the maximum residue limit (MRL) applies*: Codex MRLs for fat-soluble compounds in milk are expressed on a whole commodity basis.

Model diet*: A method used in dietary exposure assessments that assumes fixed default consumption levels, usually for categories of foods and beverages. Model diets can be based on hypothetical consumption data assuming maximum consumption amounts for broad food groups (e.g. the budget method) or can be derived from national food supply or consumption data (e.g. Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme consumption cluster diets or total diet studies). For assessing dietary exposure to residues of veterinary drugs, the Joint FAO/WHO Expert Committee on Food Additives uses a set model diet consisting of 300 g muscle (or 300 g fish muscle and skin in natural proportions), 100 g liver, 50 g kidney, 50 g tissue fat, 100 g egg, 50 g honey and 1.5 litres milk.

Muscle: The skeletal tissue of an animal carcass or cuts of these tissues from an animal carcass that contains interstitial and intramuscular fat. The muscular tissue may also include bone, connective tissue and tendons as well as nerves and lymph nodes in natural proportions. It does not include edible offal or trimmable fat.

Poultry: Any domesticated bird, including chickens, turkeys, ducks, geese, guinea-fowl or pigeons.

Residues of veterinary drugs: Include the parent compounds and/or their metabolites in any edible portion of the animal product, and include residues of associated impurities of the veterinary drug concerned.

Supervised trials median residue (STMR)*: The expected residue concentration in the food commodity (expressed in milligrams of residue per kilogram of commodity) when a pesticide has been used according to maximum good agricultural practice (GAP) conditions. The STMR is estimated as the median of the residue values (one from each trial) from supervised trials conducted according to maximum GAP conditions and includes residue components defined by the Joint FAO/WHO Meeting on Pesticide Residues for estimation of dietary intake. For some commodities, such as banana, STMR concentrations may be determined directly from concentrations measured in the edible portion when data are available.

Theoretical maximum daily intake (TMDI)*: For veterinary drugs, an estimate of dietary exposure to residues of veterinary drugs based on a specific model diet and residue concentrations at the maximum residue limit, adjusted for marker total; for pesticides, a prediction of the maximum daily intake of, for example, a pesticide residue, assuming that residues are present at the maximum residue concentrations/limits and average daily consumption of foods per person (e.g. as represented by Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme consumption cluster diets). The TMDI can be calculated for the various regional or consumption cluster diets and is expressed in milligrams of residue per person.

Tissue: All edible animal tissue, including muscle and by-products.

Total residue: For a drug in animal-derived food, the parent drug together with all the metabolites and drug-based products that remain in the food after administration of the drug to food-producing animals. The amount of total residues is generally determined by means of a study using the radiolabelled drug and is expressed as the parent drug equivalent in milligrams per kilogram of the food.

Veterinary drug: Any substance applied or administered to any food-producing animal, such as meat- or milk-producing animals, poultry, fish or bees, whether used for therapeutic, prophylactic or diagnostic purposes or for modification of physiological functions or behaviour.

Withdrawal period*: The interval between the time of the last administration of a veterinary drug and the time when the animal can be safely slaughtered for food or when milk or eggs can be safely consumed.

Annex 1

Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs

Rome, Italy, 7–11 November 2011

List of participants

Ms Janis Baines, Food Composition, Evaluation and Modelling Section, Food Standards Australia New Zealand, Canberra, Australia *(Chair)*

Professor Eloisa Dutra Caldas, Pharmaceutical Sciences Department, Faculty of Health Sciences, University of Brasilia, Brasilia, Brazil

Dr Alison Edwards, Division of Biotechnology and GRAS Notice Review, Office of Food Additive Safety, Food and Drug Administration, Department of Health and Human Services, College Park, MD, USA

Dr Lynn G. Friedlander, Office of New Animal Drug Evaluation, Division of Human Food Safety, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA

Dr Catherine Leclercq, Research Group on Food Safety Exposure Analysis, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione (INRAN), Rome, Italy

Dr David R. Tennant, Food Chemical Risk Analysis, Brighton, England

Secretariat

Dr Masami Takeuchi, Food Safety Officer, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, Rome, Italy

Dr Philippe Verger, WHO Joint Secretary to Joint FAO/WHO Meeting on Pesticide Residues, Department of Food Safety and Zoonoses, World Health Organization, Geneva, Switzerland

Ms Marla Sheffer, FAO/WHO Editor, Orleans, Ontario, Canada

Annex 2

Food and Agriculture Organization of the United Nations

World Health Organization

Report of FAO/WHO stakeholder meeting on:

Project to review and update the principles and methodology to assess dietary exposure to residues of veterinary drugs

Rome, Italy, 7 November 2011

In order to provide an opportunity for stakeholders and interested parties to present their views on the current project to review and update the principles and methodology to assess dietary exposure to residues of veterinary drugs in food, the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) issued a public announcement for a stakeholder meeting. Persons or organizations interested in participating were asked to submit a written request, and interested parties were then invited to attend the meeting.

Four of seven stakeholders participating in the meeting made presentations. The list of the stakeholders participating in this meeting is included at the end of this report. The meeting was attended by all members of the FAO/WHO meeting of experts on dietary exposure assessment methodologies (see Annex 1 for list of participants) as well as participants of the seventy-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (see Attachment 2 at the end of the stakeholder report for the list of participants). The meeting was chaired by Ms Janis Baines, and Ms Marla Sheffer acted as rapporteur. The agenda is attached at the end of the stakeholder report as Attachment 1. It should be noted that the methods proposed by the Expert Meeting were not presented and discussed at the stakeholder meeting.

Although a number of deficiencies with the existing market basket were highlighted in the presentations, stakeholders nevertheless considered that the benefits associated with the basket outweighed the deficiencies. The key findings, concerns and recommendations presented by the stakeholders with respect to potential changes to the way in which dietary exposure assessments are currently conducted by JECFA, as compiled below, were provided to the Expert Meeting on dietary exposure assessment methodologies to be considered in their discussions. It is emphasized that these are the views presented by stakeholders at the meeting and do not necessarily represent the views of FAO and WHO or other meeting participants.

Advantages of current standard food basket

- It is simple to use.
- Its conservative nature compensates for differences in diet.
- As it is not influenced by changes in regional diets, it allows for maximum residue limits (MRLs) that are harmonized across regions and across time.

- International harmonization of MRLs based on the current food basket facilitates trade.
- It provides more than adequate protection for the average consumer from long-term exposure to veterinary drug residues.

Disadvantages of current standard food basket

- It overestimates the average consumer's consumption for evaluation of chronic exposure for most commodities and age groups.
- It underestimates consumption for evaluation of acute exposure when compared with large portion size for numerous commodities in various regions, so use of the food basket may not be sufficiently protective for human health for substances for which acute toxicity is the key health concern.
- It includes only a limited number of foods.

Advantages of changing standard food basket

- Regional diets and individual consumption data would more accurately reflect actual consumption patterns.
- Improving the food basket could provide for improvements in terms of health protection.

Disadvantages of changing standard food basket

- Using regional diets and individual consumption data would be a far more complicated approach.
- It is difficult for developing countries to collect detailed food consumption data for use in deriving regional diets.
- Regional consumption factors could have a negative impact on MRL harmonization.
- The degree of uncertainty inherent in deriving acceptable daily intakes (ADIs) brings into question the logic of using precise consumption data.
- Changing the food basket would mean continual reassessment and revision of MRLs. As revised MRLs must be paralleled by revised withdrawal periods, this would entail a very heavy burden for industry and regulators, resulting in a need for additional testing. Costs associated with reviewing MRLs and withdrawal periods could lead to reduced availability of or higher prices for veterinary drugs.

Consumption of tissues not included in standard food basket

- Issues to be considered include methods for choosing tissues to be included, the need for residue data for each tissue, and the impact on MRLs for existing tissues and the portion of the ADI available for these (MRLs for existing tissues may need to be decreased and withdrawal periods increased, or ADI could be distributed between different tissues in different regions, such that MRLs would not be harmonized).
- Guideline 48 of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH) on marker residue depletion studies to establish product withdrawal periods offers scope for additional tissues and establishment of withdrawal periods.
- A new tissue could be substituted for an existing tissue in the current food basket (e.g. lung for liver). The tissues to be substituted must be appropriate for the circumstances under consideration (e.g. lung for muscle may be appropriate in certain countries).
- Alternatively, daily intake could be calculated using a single edible meat tissue (in addition to milk, eggs and honey), which would avoid the possibility of adding

numerous new tissues to a food basket, where each addition would lower the MRL in the traditional four edible tissues (muscle, kidney, liver, fat).
- Injection sites should be treated as a separate edible tissue and not as muscle.
- It is not necessary to incorporate other tissues into the food basket, as residue concentrations should not be higher than those in metabolically active tissues already included in the food basket, such as liver and kidney.

Methodology for calculating MRLs
- Regional MRLs should be avoided, as they do not facilitate international harmonization and trade.
- Calculation of MRLs needs to be reconsidered, as poorer data sets may lead to higher MRLs.

Methodology for estimating chronic and acute dietary exposure
- Median residues (for use in the calculation of the estimated daily intake, or EDI) are appropriate for evaluating chronic dietary exposure to veterinary residues.
- Although the EDI approach is more realistic for assessing chronic exposure, the minimum criteria that need to be met to allow its use are not clearly defined.
- The MRL (for use in the calculation of the theoretical maximum daily intake, or TMDI) should be used to evaluate short-term (acute) dietary exposure to veterinary residues.
- There is a need to clearly determine how to address drugs for which there are acute toxicity concerns.
- Care should be taken in acute toxicity assessment, as animal metabolism eliminates a lot of the risk (compared with the use of chemicals on plants).

Key discussion points
- JECFA is involved with risk assessment, not risk management. Therefore, the Committee takes only scientific principles into consideration in its deliberations, not social and economic consequences.
- JECFA does not support the concept (as proposed by one of the stakeholders) of "utilization of the full ADI", due to, for example, exposure from other sources and the general principle for compounds intentionally added to foods of using the lowest concentration to achieve the intended technical purpose. This position is reflected in the presentation of the ADI as a range from zero to an upper limit.
- Concern about a move to regional diets may be unjustified, as their use to provide a more accurate estimate of dietary exposure to veterinary drug residues would not result in regional MRLs being established. The Expert Meeting on dietary exposure assessment methodologies needs to better explain how the new approach, based on informed science, would work.
- It would be helpful if more countries would look at their own food consumption data to see if the data fit well with those in the food basket.
- It may be important to consider different age groups using different food baskets.
- Often only the target tissue, the one most likely to contain the chemical, is included in monitoring programmes.
- It would be helpful if radiolabel studies were designed to acquire information on concentrations in the gastrointestinal tract, lungs and oral cavity.
- The "average consumer" does not exist; in other words, no one person eats all foods at an "average" level on a daily basis. Rather, food consumption data should be chosen to protect a high proportion of the population.

- It is important to remember that the MRL is not based on the ADI, but is derived from residue depletion studies. Dietary exposure is compared with the ADI to determine whether or not an estimated MRL can be recommended. The same residue data set is used for dietary exposure assessment and estimation of MRLs in a parallel process.
- JECFA needs to consider differentiating between ADIs and acute reference doses (ARfDs) as appropriate. In some cases in the past, JECFA has derived ADIs based on acute end-points and has clearly described them as such.

List of stakeholders[1]

1. **Thomas Burnett**, International Federation for Animal Health, Brussels, Belgium
2. **Olivier Espeisse**, Corporate Affairs, Elanco Santé Animale, Suresnes, France
3. **Barbara Freischem**,* International Federation for Animal Health, Brussels, Belgium
4. **Andre Muller**,* National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
5. **Gavin Ryan**,* Committee for Medicinal Products for Veterinary Use, European Medicines Agency
6. **Laura Carina Sbordi**,* Directorate for Veterinary Products and Feed, National Directorate of Agrochemicals, Veterinary Products and Feed, SENASA (National Service for Agrifood Quality and Health), Buenos Aires, Argentina
7. **Joseph Shavila**, United Kingdom Food Standards Agency, London, England

[1] Stakeholders who gave oral presentations are marked with an asterisk (*).

Attachment 1: Stakeholder meeting agenda

Project to review and update the principles and methodology to assess dietary exposure to residues of veterinary drugs: Stakeholder meeting

FAO Rome, 7 November 2011, 9:00–15:00

The Philippines Room

Monday, 7 November 2011

Chair: Janis Baines, Rapporteur: Marla Sheffer

Time	Item	Note
09:00–09:15	Opening and welcome by FAO/WHO	Angelika Tritscher Annika Wennberg Janis Baines
09:15–09:30	Introductory presentation • Background, objectives and scope of the meeting • Expected output	Masami Takeuchi
09:30–10:00	Presentation "CVMP reflections on the current exposure assessment approach and possible developments" [European Medicines Agency's Committee for Medicinal Products for Veterinary Use (CVMP)] Q & A	Gavin Ryan
10:00–10:30	Presentation "The animal health industry's view on assessment of dietary exposure to residues of veterinary drugs" [International Federation for Animal Health (IFAH)] Q & A	Barbara Freischem
10:30–11:00	Coffee break	
11:00–11:30	Presentation "The current model diet applied by JECFA: its applicability to Argentina's national model" [Directorate for Veterinary Products and Feed, National Directorate of Agrochemicals, Veterinary Products and Feed, SENASA (National Service for Agrifood Quality and Health), Argentina] Q & A	Laura Carina Sbordi
11:30–12:00	Presentation "Comparison of the food basket with consumption data from various regions" [National Institute for Public Health and the Environment (RIVM), the Netherlands] Q & A	Andre Muller
12:00–12:45	Discussions	All
12:45–13:00	Summary and closing	FAO/WHO Janis Baines

Attachment 2: List of participants of the seventy-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives, Rome, Italy, 7–17 November 2011

Members

Professor A. Anadón, Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain

Dr D. Arnold, Consultant, Berlin, Germany *(Vice-Chairman)*

Professor A.R. Boobis, Centre for Pharmacology & Therapeutics, Department of Experimental Medicine, Division of Medicine, Faculty of Medicine, Imperial College London, London, England *(Chairman)*

Dr R. Ellis, Consultant, Myrtle Beach, SC, USA *(Joint Rapporteur)*

Dr A. Fernández Suárez, Ciencias Veterinarias, Universidad del Salvador, Buenos Aires, Argentina

Dr L.G. Friedlander, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA

Dr K.J. Greenlees, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA *(Joint Rapporteur)*

Professor J. Palermo-Neto, Department of Pathology, Faculty of Veterinary Medicine, University of São Paulo, São Paulo, Brazil

Dr L. Ritter, Canadian Network of Toxicology Centres, Professor Emeritus, School of Environmental Sciences, University of Guelph, Guelph, Ontario, Canada

Dr P. Sanders, National Reference Laboratory for Veterinary Drug Residues and Antimicrobial Resistance, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES), Fougères, France

Professor G.E. Swan, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, South Africa[1]

Secretariat

Dr J. Boison, Centre for Veterinary Drug Residues, Canadian Food Inspection Agency, Saskatoon, Saskatchewan, Canada *(FAO Expert)*

Dr A. Bruno, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Rome, Italy *(FAO Codex Secretariat)*

Dr C.E. Cerniglia, Division of Microbiology, National Center for Toxicological Research, Food and Drug Administration, Department of Health and Human Services, Jefferson, AR, USA *(WHO Temporary Adviser)*

[1] Dr Swan was invited but unable to attend the meeting.

Dr P.L. Chamberlain, Office of the Chief/Office of the Chief Scientist/Office of Counterterrorism and Emerging Threats, Food and Drug Administration, Department of Health and Human Services, Silver Spring, MD, USA *(WHO Temporary Adviser)*

Dr S. Ghimire, Veterinary Drugs Directorate, Health Canada, Ottawa, Ontario, Canada *(WHO Temporary Adviser)*

Dr N. Jarrett, European Medicines Agency, London, England *(WHO Temporary Adviser)*

Professor S.H. Jeong, Department of Applied Biotoxicology, Hoseo University, Hoseo Toxicology Research Centre, Asan City, Chungnam, Republic of Korea *(WHO Temporary Adviser)*

Professor B. Le Bizec, Laboratoire d'Étude des Résidus et des contaminants dans les aliments (LABERCA), École Nationale Vétérinaire, Agroalimentaire et de l'Alimentation Nantes Atlantique (ONIRIS), Nantes, France *(FAO Expert)*

Dr K. Ogawa, Division of Pathology, Biological Safety Research Center, National Institute of Health Sciences, Tokyo, Japan *(WHO Temporary Adviser)*

Dr F. Ramos, Bromatology, Pharmacognosy and Analytical Sciences Group, Pharmacy Faculty, Coimbra University, Coimbra, Portugal *(FAO Expert)*

Dr G. Roberts, Consultant, Preston, Victoria, Australia *(WHO Temporary Adviser)*

Ms M. Sheffer, Orleans, Ontario, Canada *(FAO/WHO Editor)*

Dr A. Tritscher, Department of Food Safety and Zoonoses, World Health Organization, Geneva, Switzerland *(WHO Joint Secretary)*

Dr P. Verger, Department of Food Safety and Zoonoses, World Health Organization, Geneva, Switzerland *(WHO Joint Secretary to Joint FAO/WHO Meeting on Pesticide Residues)*

Dr A. Wennberg, Nutrition and Consumer Protection Division, Food and Agriculture Organization of the United Nations, Rome, Italy *(FAO Joint Secretary)*

Annex 3

Summary of food consumption data submitted, by country[a]

Country[b]	Name of study	Survey period	Food raw or as consumed	Age range (years)	No. of survey days	Food consumption, C-only (g/person per day)	Food consumption, Total pop (g/person per day)	Food consumption, C-only (g/kg bw per day)	Food consumption, Total pop (g/kg bw per day)	Person-day data available
Individual-based survey data submitted to JECFA[c]										
Argentina	General Rodriguez* (*n* = 236); Mar del Plata* (*n* = 199)	?	?	18–65	30 (FFQ)		√			
Australia	NNS of Australia (*n* = ~14 000)	1995	Raw	2+, 2–6	1	√	√	√	√	√
	NCNPAS (*n* = ~5000)	2007	Raw	2–16	2	√	√			
Austria (EFSA)	ASNS (*n* = 2123)	2005–2006	As consumed	19–65	1			√	√	√
Belgium (EFSA)	Regional Flanders* (*n* = 661)	2002–2003	Mixed	2.5–6.5	3	√	√	√	√	√
	Diet National 2004 (*n* = 3245)	2004–2005	As consumed	>15	2	√	√	√	√	√
Brazil	Pesquisa de Orcamento Familiar (*n* = 34 003)	2008–2009	Raw	≥10	2	√	√	√	√	√
Bulgaria (EFSA)	NSFIN (*n* = 1204)	2004	Raw	>16	1	√	√	√	√	√
	NUTRICHILD (*n* = 1723)	2007	Mixed	<5	2	√	√	√	√	√
Cambodia	Regional* (*n* = 941)	?	As consumed	25–65	2	√	√			

Country[b]	Name of study	Survey period	Food raw or as consumed	Age range (years)	No. of survey days	Food consumption, C-only (g/person per day)	Food consumption, Total pop (g/person per day)	Food consumption, C-only (g/kg bw per day)	Food consumption, Total pop (g/kg bw per day)	Person-day data available
China	National Nutrition and Health Survey (*n* = 69 205)	2002	As consumed	All ages, 2–6	1	√	√			√
	Hong Kong SAR Population-Based Food Consumption Survey* (*n* = ~5000)	2005–2007	As consumed	20–84	2	√	√			
Cyprus (EFSA)	Childhealth (*n* = 303)	2003	Mixed	11–18	3	√	√	√	√	√
Czech Republic (EFSA)	SISP04 (*n* = 1751)	2003–2004	Raw	>4	2	√	√	√	√	√
Denmark (EFSA)	Danish Dietary Survey (*n* = 4118)	2000–2002	Raw	4–75	7	√	√	√	√	√
Estonia (EFSA)	NDS 1997 (*n* = 1866)	1997	Mixed	19–64	1			√	√	√
Finland (EFSA)	FINDIET 2007 (*n* = 2038)	2007	Raw	25–74	1	√	√	√	√	√
	DIPP* (*n* = 1448)	2003–2006	Mixed	1, 3, 6	3	√	√	√	√	√
	STRIP* (*n* = 250)	2000	Mixed	7–8	4	√	√	√	√	√
France (EFSA)	INCA2 (*n* = 4079)	2005–2007	As consumed	3–79	7	√	√	√	√	√
Germany (EFSA)	DONALD* (*n* = 926)	2006–2008	Mixed	1–10	3					√
	National Nutrition Survey II (*n* = 13 926)	2005–2007	As consumed	14–80	2	√	√	√	√	√

Country[b]	Name of study	Survey period	Food raw or as consumed	Age range (years)	No. of survey days	Food consumption, C-only (g/person per day)	Food consumption, Total pop (g/person per day)	Food consumption, C-only (g/kg bw per day)	Food consumption, Total pop (g/kg bw per day)	Person-day data available
Greece (EFSA)	Regional Crete* (*n* = 874)	2004–2005	Mixed	4–6	3	√	√	√	√	√
Hungary (EFSA)	National Representative Survey (*n* = 1360)	2003	Raw	>18	3	√	√	√	√	√
Ireland (EFSA)	NSIFCS (*n* = 958)	1997–1999	Raw	18–64	7	√	√	√	√	√
Italy (EFSA)	INRAN-SCAI (*n* = 3323)	2005–2006	Raw	>0.1	3	√	√	√	√	√
Japan	National Health and Nutrition Survey (*n* = ~18 000)	2009	As consumed	1+, <15, ≥15	1	√	√			√
Latvia (EFSA)	EFSA_TEST (*n* = 2070)	2008	As consumed	7–66	2	√	√	√	√	√
Netherlands (EFSA)	VCP_kids (*n* = 279)	2005–2006	Raw	2–6	3	√	√	√	√	√
	DNFCS-2003 (*n* = 750)	2003	Raw	19–30	2	√	√	√	√	√
Poland (EFSA, other)	IZZ-FAO-2000 (*n* = 4134)	2000	Raw	1–96	1	√	√	√	√	√
	Household Budget Survey	2008	Raw	18+	?		√[d]			
Slovakia (EFSA)	SK MON 2008 (*n* = 2761)	2008	Mixed	19–59	1			√	√	√
Slovenia (EFSA)	CRP-2008 (*n* = 410)	2007–2008	As consumed	18–65	1			√	√	√
Spain (EFSA)	enKid (*n* = 382)	1998–2000	Mixed	1–14	2	√	√	√	√	√
	NUT-INK05* (*n* = 1050)	2004–2005	Mixed	4–18	2	√	√	√	√	√

Country[b]	Name of study	Survey period	Food raw or as consumed	Age range (years)	No. of survey days	Food consumption, C-only (g/person per day)	Food consumption, Total pop (g/person per day)	Food consumption, C-only (g/kg bw per day)	Food consumption, Total pop (g/kg bw per day)	Person-day data available
	AESAN-FIAB (*n* = 1068)	1999–2001	As consumed	17–60	3	√	√	√	√	√
	AESAN (*n* = 418)	2009	As consumed	18–60	2	√	√	√	√	√
Sweden (EFSA)	NFA (*n* = 2495)	2003	As consumed	3–18	4	√	√	√	√	√
	RIKSMATEN (*n* = 1210)	1997–1998	As consumed	18–74	7	√	√	√	√	√
Thailand	National Consumer Survey (*n* = 18 998)	2004–2005	Raw	3+	30 (FFQ)		√			
United Kingdom (EFSA)	NDNS (*n* = 1724)	2000–2001	As consumed	19–64	7	√	√	√	√	√
USA	NHANES (*n* = ~20 000)	2003–2006	Raw	2+, 2–6	2	√	√	√	√	√
Viet Nam	Nationwide survey (*n* = 8267)	2009	?	All ages	?		√			
Household-level survey data submitted to JECFA										
Brazil	Household Budget Survey (*n* = 55 970)	2008–2009	Mixed	All ages	2		√			
Cameroon	National Nutrition and Health Survey (*n* = 69 205)	2002	Mixed	2+	15	√ (?)	√ (?)			
Food balance sheet (poundage) data from Latin America										
Argentina		2000–2010	Raw				√			
Bolivia (Plurinational		2000, 2009	Raw				√			

Country[b]	Name of study	Survey period	Food raw or as consumed	Age range (years)	No. of survey days	Food consumption, C-only (g/person per day)	Food consumption, Total pop (g/person per day)	Food consumption, C-only (g/kg bw per day)	Food consumption, Total pop (g/kg bw per day)	Person-day data available
State of)										
Chile		2000–2010	Raw				√			
Colombia		2008–2009	Raw				√			
Costa Rica		2009	Raw				√			
Ecuador		2008–2010	Raw				√			
El Salvador		2000, 2009	Raw				√			
Guatemala		2009	Raw				√			
Honduras		2009	Raw				√			
Mexico		2009–2010	Raw				√			
Nicaragua		2009	Raw				√			
Panama		2009	Raw				√			
Paraguay		?	Raw				√			
Peru		2000–2010	Raw				√			
Uruguay		2004–2009	Raw				√			
Venezuela (Bolivarian Republic of)		2004, 2009	Raw				√			

AESAN, Spanish Food Safety and Nutrition Authority; ASNS, Austrian Study on Nutritional Status; bw, body weight; C-only, consumers only; CRP, Central Register of Population; DIPP, Finnish Type I Diabetes Prediction and Prevention Study; DNFCS, Dutch National Food Consumption Survey; DONALD, Dortmund Nutritional and Anthropometric Longitudinally Designed Study; enKid, population-based cross-sectional study carried out on a random sample of the Spanish population aged 2–24 years; FFQ, food frequency questionnaire; FIAB, Spanish Food and Drink Industry Federation; INCA, Enquête Individuelle et Nationale sur les Consommations Alimentaires; INRAN-SCAI, Italian National Food Consumption Survey; IZZ-FAO, Food and Nutrition Institute–Food and Agriculture Organization of the United Nations; NCNPAS, National Children's Nutrition and Physical Activity Survey; NDNS, National Diet and Nutrition Survey; NDS, National Diet Survey; NFA, National Food Administration; NHANES, National Health and Nutrition Examination Survey; NNS, National Nutrition Survey; NSFIN, National Survey of Food Intake and Nutritional Status; NSIFCS, North/South Ireland Food Consumption Survey; NUT-INK, Nutrition Survey of the Basque Population; RIKSMATEN, National Food Survey; SAR, Special Administrative Region; SISP, Individual Food

Consumption – the National Survey; SK MON, Monitoring of Nutritional Status of Slovak Citizens; STRIP, Special Turku Coronary Risk Factor Intervention Project; Total pop, total population; VCP, Voedselconsumptiepeiling onder jongvolwassenen

[a] "√" indicates whether data were submitted.

[b] "(EFSA)" indicates that data were submitted by EFSA, not by the individual country.

[c] Surveys marked with an asterisk (*) are regional.

[d] Data from Poland's 2008 survey are expressed in consumption units normalized to an adult male as the consumption unit.

Annex 4

Comparison between distributional approach and two models for chronic dietary exposure estimates

Two deterministic approaches to modelling chronic dietary exposure were discussed.

In the first method, the highest 97.5th percentile dietary exposure (calculated considering consumers only) from each food category is added to the mean dietary exposure from all other foods (all subjects) in the diet to estimate the total dietary exposure of high-level consumers of each food type.

Highest plus mean of rest of diet approach (Method A):

High-level exposure from each animal product	=	**97.5th percentile consumption**	×	**Median residue**
(mg/kg body weight per day or mg/day)		(kg/kg body weight per day or kg/day)		(mg/kg)
Chronic dietary exposure	=	**Highest exposure from one animal product**	+	**Total mean exposure from all other products**
(mg/kg body weight per day or mg/day)		(mg/kg body weight per day or mg/day)		(mg/kg body weight per day or mg/day)

A more conservative version of this approach consists of summing the 97.5th percentile of exposure for the two highest categories that are the main contributors with the mean exposure for the other categories.

Two highest plus mean of rest of diet approach (Method B):

High-level exposure from each animal product	=	**97.5th percentile consumption**	×	**Median residue**
(mg/kg body weight per day or mg/day)		(kg/kg body weight per day or kg/day)		(mg/kg)
Chronic dietary exposure	=	**Highest exposures from two animal products**	+	**Total mean exposure from all other products**
(mg/kg body weight per day or mg/day)		(mg/kg body weight per day or mg/day)		(mg/kg body weight per day or mg/day)

The algorithm used in the chronic model has been explored by taking JECFA MRL values[1] and comparing the results obtained with the two possible methods (highest plus mean of rest of diet or two highest plus mean of rest of diet) with the results based on the same food consumption data but using a distributional model. In the distributional model, each individual's dietary exposure is calculated, and then the population mean and percentiles are

[1] http://www.fao.org/ag/agn/jecfa-vetdrugs/results.html?vetdrugName=&status=MRL_F&techFunction=&searchBy=astatus

estimated from the distribution. The same food categories and residue concentrations are used in both models. MRL values used in all models are provided in Table A4-1.

This comparative exercise was undertaken prior to the Expert Meeting and relates to the chronic model where individual records of food consumption data from the United Kingdom were used. It did not include the new data obtained through the FAO/WHO meeting of experts reported elsewhere in this report. Chronic dietary exposures were calculated using Methods A and B and also by a distributional model. The distributional model estimated dietary exposure for each individual in the United Kingdom survey, and then the population mean and high percentile values were derived from these individual results. The same food categories and residue concentrations were used in each model. In this preliminary exercise, the high percentile value selected for Methods A and B and the distributional model was the 95th percentile.

The results of the comparative exercise for nine veterinary drug MRLs are summarized in Table A4-2. Both Methods A and B appear to provide a reliable prediction of the 95th percentile dietary exposure derived from the distribution of actual records of individual exposures, apart from cases where residues are present in a small number of tissues (clenbuterol and zeranol), where they both overestimate the exposure calculated using the distributional approach by a large margin. Results are presented graphically without (Figure A4-1) and with (Figure A4-2) body weight correction.

Given the uncertainties inherent in the methods and the underlying conservative assumptions within the data (i.e. all food products can contain residues and maximum concentrations), the "highest plus mean from rest of the diet" method is probably the preferred approach, because it gives a result close to the value that would be obtained in a distributional model and it is relatively simple to apply.

Table A4-1. JECFA MRL values used in comparative exercise

Dihydrostreptomycin			Chlortetracycline			Oxfendazole			Sulfadimidine			Zeranol			Monensin		
Cattle	Muscle	600	Cattle	Muscle	200	Cattle	Muscle	100	Cattle	Muscle	100	Cattle	Muscle	2	Cattle	Muscle	10
Cattle	Liver	600	Cattle	Liver	600	Cattle	Liver	500	Cattle	Liver	100	Cattle	Liver	10	Cattle	Liver	20
Cattle	Kidney	1000	Cattle	Kidney	1200	Cattle	Kidney	100	Cattle	Kidney	100				Cattle	Kidney	10
Cattle	Fat	600	Cattle	Milk	100	Cattle	Fat	100	Cattle	Fat	100	**Ivermectin**			Cattle	Fat	100
Cattle	Milk	200	Sheep	Muscle	200	Cattle	Milk	100	Cattle	Milk	25	Cattle	Liver	100	Cattle	Milk	2
Sheep	Muscle	600	Sheep	Liver	600	Sheep	Muscle	100	Sheep	Muscle	100	Cattle	Fat	40	Sheep	Muscle	10
Sheep	Liver	600	Sheep	Kidney	1200	Sheep	Liver	500	Sheep	Liver	100	Cattle	Milk	10	Sheep	Liver	20
Sheep	Kidney	1000	Sheep	Milk	100	Sheep	Kidney	100	Sheep	Kidney	100	Sheep	Liver	15	Sheep	Kidney	10
Sheep	Fat	600	Pig	Muscle	200	Sheep	Fat	100	Sheep	Fat	100	Sheep	Fat	20	Sheep	Fat	100
Sheep	Milk	200	Pig	Liver	600	Sheep	Milk	100	Pig	Muscle	100	Pig	Liver	15	Chicken	Muscle	10
Pig	Muscle	600	Pig	Kidney	1200	Pig	Muscle	100	Pig	Liver	100	Pig	Fat	20	Chicken	Liver	10
Pig	Liver	600	Poultry	Muscle	200	Pig	Liver	500	Pig	Kidney	100				Chicken	Kidney	10
Pig	Kidney	1000	Poultry	Liver	600	Pig	Kidney	100	Pig	Fat	100	**Clenbuterol**			Chicken	Fat	100
Pig	Fat	600	Poultry	Kidney	1200	Pig	Fat	100	Poultry	Muscle	100	Cattle	Muscle	0.2	Goat	Muscle	10
Chicken	Muscle	600	Poultry	Eggs	400	Horse	Muscle	100	Poultry	Liver	100	Cattle	Liver	0.6	Goat	Liver	20
Chicken	Liver	600			µg/kg	Horse	Liver	500	Poultry	Kidney	100	Cattle	Kidney	0.6	Goat	Kidney	10
Chicken	Kidney	1000				Horse	Kidney	100	Poultry	Fat	100	Cattle	Fat	0.2	Goat	Fat	100
Chicken	Fat	600	**Erythromycin A**			Horse	Fat	100			µg/kg	Cattle	Milk	0.05	Turkey	Muscle	10
		µg/kg	Chicken	Muscle	100	Goat	Muscle	100				Horse	Muscle	0.2	Turkey	Liver	10
			Chicken	Liver	100	Goat	Liver	500				Horse	Liver	0.6	Turkey	Kidney	10
			Chicken	Kidney	100	Goat	Kidney	100				Horse	Kidney	0.6	Turkey	Fat	100
			Chicken	Fat	100	Goat	Fat	100				Horse	Fat	0.2	Quail	Muscle	10
			Chicken	Eggs	50			µg/kg						µg/kg	Quail	Liver	10
			Turkey	Muscle	100										Quail	Kidney	10
			Turkey	Liver	100										Quail	Fat	100
			Turkey	Kidney	100												µg/kg
			Turkey	Fat	100												
					µg/kg												

Table A4-2. Results of comparative exercise for estimating chronic dietary exposure[a]

	Deterministic model						Distributional model				Ratios[b]	
	µg/day			µg/kg bw per day			µg/day		µg/kg bw per day		Method A	Method B
Residue	Pop mean	Method A	Method B	Pop mean	Method A	Method B	Mean	P95	Mean	P95	/ P95	/ P95
Clenbuterol	0.017	0.120	0.135	0.0002	0.0015	0.0018	0.017	0.035	0.0002	0.0005	3.2	3.7
Dihydrostreptomycin	93.3	153.7	190.4	1.25	2.11	2.61	93.3	174.3	1.25	2.35	0.9	1.1
Chlortetracycline	48.1	89.6	119.9	0.65	1.16	1.59	48.1	86.9	0.65	1.19	1.0	1.3
Oxfendazole	29.5	59.7	81.4	0.40	0.83	1.12	29.5	60.7	0.40	0.82	1.0	1.4
Sulfadimidine	13.8	21.4	27.5	0.19	0.29	0.38	13.9	26.0	0.19	0.34	0.9	1.1
Zeranol	0.041	0.438	0.546	0.0005	0.0056	0.0070	0.059	0.152	0.0008	0.0020	2.9	3.6
Ivermectin	4.56	9.95	13.92	0.061	0.131	0.181	4.57	9.93	0.061	0.132	1.0	1.4
Monensin	1.28	2.14	2.91	0.017	0.029	0.039	1.27	2.47	0.017	0.033	0.9	1.2
Erythromycin A	3.9	10.1	14.3	0.05	0.14	0.19	4.0	9.9	0.05	0.13	1.0	1.5
Avilamycin	11.0	23.2	33.6	0.15	0.31	0.44	11.4	25.7	0.15	0.34	0.9	1.3

bw, body weight; P95, 95th percentile; Pop mean, general population mean dietary exposure

[a] Method A, Sum of highest exposure at 95th percentile (consumers only) for one food and general population mean exposure for all other foods; Method B, Sum of highest exposure at 95th percentile (consumers only) for two foods and general population mean exposure for all other foods.

[b] Ratio of estimated dietary exposure using Method A or B to the 95th percentile dietary exposure estimate derived from individual dietary records using the distributional model.

Figure A4-1. Comparison of deterministic and distributional models without body weight correction

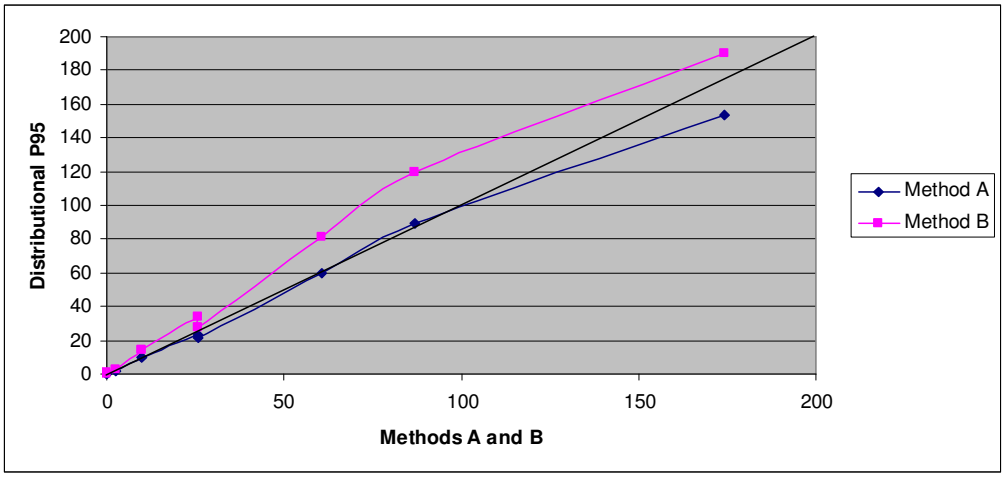
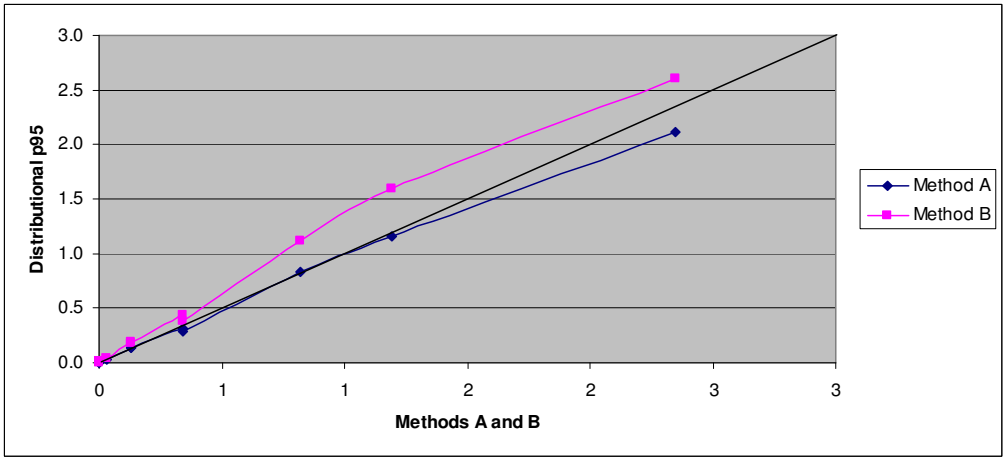


Figure A4-2. Comparison of deterministic and distributional models with body weight correction



Annex 5

Food consumption data for the general population aged 2+ years

Table A5-1. Mean food consumption for the general population aged 2+ years[a]

Part A: Argentina to Honduras

Food type as raw commodity	Food consumption (g/person per day)																	
	Argentina	Australia	Belgium	Bolivia (Plurinational State of)	Brazil	Chile	China	Colombia	Costa Rica	Czech Republic	Denmark	Ecuador	El Salvador	Finland	France	Germany	Guatemala	Honduras
Mammalian muscle																		
Beef and other bovines	196	79		55	97	62	4	47	51			27						
Pork and other porcines	26	46		16	12	66	48	12	30			23						
Sheep and other ovines	16	25		12	0.5	0.8												
Goat and other caprines					0.8		0.01											
Horse and other equines																		
Rabbit																		
All mammalian muscle		124	44				56			57	80			38	64	34		
Mammalian trimmed fat, skin and added fat			5							21	16			4	12	10		

Food type as raw commodity	Food consumption (g/person per day)																	
	Argentina	Australia	Belgium	Bolivia (Plurinational State of)	Brazil	Chile	China	Colombia	Costa Rica	Czech Republic	Denmark	Ecuador	El Salvador	Finland	France	Germany	Guatemala	Honduras
Mammalian offal		1																
Mammalian liver					2.3 (bovine)													
Mammalian kidney																		
Mammalian lung																		
All mammalian offal			0.4		11.6					4	0.8			1	3	0.9		
Fish and seafood																		
Fish			17							16	15			25	21	13		
Crustaceans		2	4		0.7					0.1	2			0.9	2	0.6		
Molluscs		2	2							0	0.1			0.2	3	0.4		
All fish and seafood	8	24	26		25	82		18		17	18	19		26	30	17		
Poultry muscle	99	164	22	82	51	217	12	64	71	37	25	71	51	30	31	16	62	50
Poultry fat and skin																		
Poultry offal		0.51	0.4		0.2					4	0.8			1	3	0.9		
Eggs (all)		17	10	16	17	24	22	26	32	20	16	17	28	16	15	12	24	16
Milk[b]	544	758	172	119	178	382	10		540	172	376	283		451	205	185		
Honey	0.55	3	10		0.3	0.22		0.2		5	0.4		0.27	4	4	8		

[a] The values provided are assumed to apply to the general population aged 2 years and over; however, some of the data sets submitted did not cover this specific age range (see Annex 3 for details).

[b] Includes whole liquid milk, secondary milk products (e.g. skimmed milk, evaporated milk, milk powders), derived milk products (e.g. cream, butter) and manufactured milk products (yoghurt, cheese, ice cream).

Table A5-1. Mean food consumption for the general population aged 2+ years[a]

Part B: Hungary to Venezuela (Bolivarian Republic of)

Food type as raw commodity	Food consumption (g/person per day)																	
	Hungary	Ireland	Italy	Japan	Latvia	Mexico	Netherlands	Nicaragua	Panama	Paraguay	Peru	Poland	Spain	Sweden	United Kingdom	Uruguay	USA	Venezuela (Bolivarian Republic of)
Mammalian muscle																		
Beef and other bovines						49					14					159	41	66
Pork and other porcines						41										13	26	13
Sheep and other ovines						0.7					12						0.5	
Goat and other caprines																		
Horse and other equines																		
Rabbit																		
All mammalian muscle	60	70	61	79	63		55						61	27	35		77	
Mammalian trimmed fat, skin and added fat	10	10	3	10	7		2						6	2	4			

Food type as raw commodity	Food consumption (g/person per day)																	
	Hungary	Ireland	Italy	Japan	Latvia	Mexico	Netherlands	Nicaragua	Panama	Paraguay	Peru	Poland	Spain	Sweden	United Kingdom	Uruguay	USA	Venezuela (Bolivarian Republic of)
Mammalian offal																	0.4	
Mammalian liver																		
Mammalian kidney																		
Mammalian lung																		
All mammalian offal	10	1 (M+P)	1 (M+P)		3 (M+P)		0.4 (M+P)						2 (M+P)	1 (M+P)	2 (M+P)			
Fish and seafood																		
Fish	9	20	31		16		5						57	17	22			
Crustaceans	0	0.8	4		0		1						5	4	3		3	
Molluscs	0	0.2	10		0.0		0.4						12	0.1	0.5		0.7	
All fish and seafood	9	21	46	79	18		9						75	33	27	30	16	30
Poultry muscle	44	42	21		23	74	24	43	95		88		33	7	37	52	126	95
Poultry fat and skin																		
Poultry offal	10	1	1		3		0.4						2	1	2		0.2	
Eggs (all)	26	20	21	35	9	49	12	11	16		19		29	12	5		24	18
Milk[b]	260	303	186	96	138	350	359			93	180		378	359	260	650	296	340
Honey	8	5			6	1	4							3	3		0.76	

M+P, mammalian plus poultry

[a] The values provided are assumed to apply to the general population aged 2 years and over; however, some of the data sets submitted did not cover this specific age range (see Annex 3 for details).

[b] Includes whole liquid milk, secondary milk products (e.g. skimmed milk, evaporated milk, milk powders), derived milk products (e.g. cream, butter) and manufactured milk products (yoghurt, cheese, ice cream).

Table A5-2. Chronic 97.5th percentile food consumption for the general population aged 2+ years[a]

Food type as raw commodity	Belgium	Brazil	China (Hong Kong SAR)	Czech Republic	Denmark	Finland	France	Germany	Hungary	Ireland	Italy	Japan	Latvia	Netherlands	Spain	Sweden	United Kingdom	USA
Mammalian muscle																		
Beef and other bovines		325	150															182.5
Pork and other porcines		428	189.9															142
Sheep and other ovines		373	121.5															146.3
Goat and other caprines		401																169.4
Horse and other equines																		
Rabbit																		
All mammalian muscle	247.5			257.1	200	219.1	168.7	238.5	191.7	206.5	200	265.4	300.0	250	264.8	91.4	120.9	264
Mammalian trimmed fat, skin and added fat	70		14.7	70	54	19.6	42.6	65	52.7	57.3	24.7	33.9	50.0	36.9	30	34.3	27.2	53.1
Mammalian offal																		
Mammalian liver		203 *(bovine)*																102.7
Mammalian kidney																		102.3 *(includes kidney)*
Mammalian lung																		
All mammalian offal	112.5 (M+P)		12.86	126.3 (M+P)	61.8 (M+P)	95.2 (M+P)	50 (M+P)	175 (M+P)	111.3 (M+P)	62.7 (M+P)	128.7 (M+P)		125.0 (M+P)	93.8 (M+P)	115.8 (M+P)	38.6 (M+P)	41.7 (M+P)	34.7
Fish and seafood																		
Fish	183.2	1000	250	225	62	195.3	85.9	190.2	200	97.1	132.3		200.0	110.7	206.7	86.4	92.9	178.1
Crustaceans	117.5	376	185.8	75	22.9	75.0	18.5	109.4	26.7	24.7	134.6		35.0	150	97.8	51.4	37	167.4

Food type as raw commodity	Belgium	Brazil	China (Hong Kong SAR)	Czech Republic	Denmark	Finland	France	Germany	Hungary	Ireland	Italy	Japan	Latvia	Netherlands	Spain	Sweden	United Kingdom	USA
Molluscs	125	190	100		70.6	80.0	46.1	325		35.8	152.7		0	45.4	197.5	57.1	56.1	164.5
All fish and seafood	206.3			225	68.1	195.3	100.2	199	200	100.8	195.2	264.2	200.0	150	237.5	94.3	105.9	191.1
Poultry muscle	170.9	300	182	230.8	92.8	262.7	133.8	214.3	166.7	133.3	124.4		230.0	243.8	212.4	47.1	115.5	213.2
Poultry fat and skin																		
Poultry offal	112.5 (M+P)	188		126.3 (M+P)	61.8 (M+P)	95.2 (M+P)	50 (M+P)	175 (M+P)	111.3 (M+P)	62.7 (M+P)	128.7 (M+P)		125.0 (M+P)	93.8 (M+P)	115.8 (M+P)	38.6 (M+P)	41.7 (M+P)	68.2
Eggs (all)	95	150	80	97.6	54	96.1	54.2	90	90	51.4	91.4	120.0	110.0	63.4	86.4	57.1	72.9	113.7
Milk[b]	581.3	600	351.8	591.1	1056.6	1235.5	576.1	672.2	744.7	781.6	444.8	551.9	560.0	1018.7	858.3	900.0	670.4	1018
Honey	140	100		35	2.7	30.1	32	50	73.7	42.9	40		55.0	10	33.3	27.9	28.1	21.8

M+P, mammalian plus poultry; SAR, Special Administrative Region

[a] The values provided are assumed to apply to the general population aged 2 years and over; however, some of the data sets submitted did not cover this specific age range (see Annex 3 for details).

[b] Includes whole liquid milk, secondary milk products (e.g. skimmed milk, evaporated milk, milk powders), derived milk products (e.g. cream, butter) and manufactured milk products (yoghurt, cheese, ice cream).

Annex 6

Food consumption data for children aged 2–6 years

Table A6-1. Mean food consumption for children aged 2–6 years

	Food consumption (g/person per day)														
Food type as raw commodity	Australia (2–6 years)	Belgium (2–6 years)	Bulgaria (3–<5 years)	China (2–6 years)	Czech Republic (4–9 years)	Denmark (4–9 years)	France (3–9 years)	Germany (3–9 years)	Greece (3–9 years)	Italy (3–9 years)	Japan (1–6 years)	Netherlands (3–6 years)	Spain (3–9 years)	Sweden (3–9 years)	USA (2–6 years)
Mammalian muscle															
Beef and other bovines	39.2			2											19.8
Pork and other porcines	24.8			28.1											13.9
Sheep and other ovines	12.7			2.1											0.09
Goat and other caprines															0
Horse and other equines				0.2											0
Rabbit															
All mammalian muscle	56.9	12;4	31.1		31.2	50.9	41.6	9.6	22.7	50.9	61.8 (all meats)	10	40.1	16.9	39.6
Mammalian trimmed fat, skin and added fat	2.9	0.5 (all fats)[a]	8.2 (all fats)[a]		1.9 (all fats)[a]	0.2 (all fats)[a]	0.6 (all fats)[a]	0 (all fats)[a]	0.1 (all fats)[a]	2.5 (all fats)[a]	7.9 (all fats)[a]	0 (all fats)[a]	1.1 (all fats)[a]	0.2 (all fats)[a]	9.3

Food type as raw commodity	Food consumption (g/person per day)														
	Australia (2–6 years)	Belgium (2–6 years)	Bulgaria (3–<5 years)	China (2–6 years)	Czech Republic (4–9 years)	Denmark (4–9 years)	France (3–9 years)	Germany (3–9 years)	Greece (3–9 years)	Italy (3–9 years)	Japan (1–6 years)	Netherlands (3–6 years)	Spain (3–9 years)	Sweden (3–9 years)	USA (2–6 years)
Mammalian offal															
Mammalian liver	0.01														0.04
Mammalian kidney	0.05														
Mammalian lung															
All mammalian offal	0.22	1.5	1.2 (M+P)	74.4	1.9	0.2	0.6	0	0.2 (M+P)	0.7 (M+P)		0	0.7 (M+P)	0	0.16
Fish and seafood															
Fish	7.1	5.9	6.7		10.6	10.1	11.3	4.2	10.7	21.7		2.2	30.8	7.9	4.2
Crustaceans	0.22	0.3	0		0	0.8	0.6	0	0.2	2.4		0	1.1	0.4	0.7
Molluscs	0.26	0.1	0		0	0	0.6	0	2	0.8		0	3.1	0.1	0.14
All fish and seafood		9.1	6.7		11.6	12.2	20.7	9.9	13	40.2	35.9	5.2	36.5	15.6	5
Poultry muscle	17.2	8	32.3	8.4	32.2	15.9	20	7.1	11	11.6		5.7	36.5	11.5	29.3
Poultry fat and skin															
Poultry offal	0.12	1.5	1.2 (M+P)	260.7	1.9	0.2	0.6	0	0.2 (M+P)	0.7 (M+P)		0	0.7 (M+P)	0	0.08
Eggs (all)	9.1	0	13.6	18.7	15.8	12.7	11.7	11.6	6.9	19.9	27.9	5.6	0.5	3.6	15.9
Milk[a]	634	428	234	16.9	281	528	308	284	360	259	199.3	416	487	470	446.4
Honey	1.7	1.9	3.1		5	0.4	2.5	4.1				1.9		1.3	0.4

bw, body weight; M+P, mammalian plus poultry

[a] All animal oils and fats.

[b] Includes whole liquid milk, secondary milk products (e.g. skimmed milk, evaporated milk, milk powders), derived milk products (e.g. cream, butter) and manufactured milk products (yoghurt, cheese, ice cream).

Table A6-2. Chronic 97.5th percentile food consumption for children aged 2–6 years

	Food consumption (g/person per day)											
Food type as raw commodity	Belgium (2–6 years)	Bulgaria (3–<5 years)	Czech Republic (4–9 years)	Denmark (4–9 years)	France (3–9 years)	Germany (3–9 years)	Greece (4–6 years)	Italy (3–9 years)	Netherlands (3–6 years)	Spain (3–9 years)	Sweden (3–9 years)	USA (2–6 years)
Mammalian muscle												
Beef and other bovines												88.3
Pork and other porcines												90.3
Sheep and other ovines												
Goat and other caprines												
Horse and other equines												
Rabbit												
All mammalian muscle	68	112.5	144	114	112	79.7	100	141	65	145	59.3	126
Mammalian trimmed fat, skin and added fat	20 (all fats)[a]	24.8 (all fats)[a]	48.7 (all fats)[a]	38.3 (all fats)[a]	23.8 (all fats)[a]	24.6 (all fats)[a]	6.7 (all fats)[a]	20.8 (all fats)[a]	16.3 (all fats)[a]	17.5 (all fats)[a]	13.8 (all fats)[a]	30.1
Mammalian offal												
Mammalian liver												
Mammalian kidney												
Mammalian lung												
All mammalian offal	62 (M+P)	104.9 (M+P)	109.4 (M+P)	34 (M+P)	18.6 (M+P)	9.5 (M+P)	6.7 (M+P)	20.8 (M+P)	0 (M+P)	17.5 (M+P)	0	6.3
Fish and seafood												
Fish	62	100.2	115	46	47	74.6	83.3	114	87.5	175	50	85.7
Crustaceans	17	0	0	18.2	11	16.7	33.3	88.1	124	45	25	92.4
Molluscs	29	0	5	3.5	33	0	83.3	216	10	100	37.5	
All fish and seafood	73	100.2	115	47.3	64.8	75.3	100	181	91.4	160	61.3	94.5
Poultry muscle	57	132.3	207	65	65.7	66.8	73.3	110.9	250	157	58.3	123.9

Food type as raw commodity	Food consumption (g/person per day)											
	Belgium (2–6 years)	Bulgaria (3–<5 years)	Czech Republic (4–9 years)	Denmark (4–9 years)	France (3–9 years)	Germany (3–9 years)	Greece (4–6 years)	Italy (3–9 years)	Netherlands (3–6 years)	Spain (3–9 years)	Sweden (3–9 years)	USA (2–6 years)
Poultry fat and skin												
Poultry offal	62 (M+P)	104.9 (M+P)	109.4 (M+P)	34 (M+P)	18.6 (M+P)	9.5 (M+P)	6.7 (M+P)	20.8 (M+P)	0 (M+P)	17.5 (M+P)	0	179.5 (M+P)
Eggs (all)	17		72	35.8	46.5	54..6	50	115	50	30	37.5	87.7
Milk[b]	980	581.2	614	107	661	795	813	531	962	907	895	1065
Honey	25	17.3	35	2.4	22.6	26.3	21.5	23.3	35	84	15.8	14

M+P, mammalian plus poultry

[a] All animal oils and fats.

[b] Includes whole liquid milk, secondary milk products (e.g. skimmed milk, evaporated milk, milk powders), derived milk products (e.g. cream, butter) and manufactured milk products (yoghurt, cheese, ice cream).

Annex 7

Canadian proposal for simplification of the exposure assessment model

Canada proposes a simplified model for exposure assessment utilizing the food consumption data reviewed and methodology proposed in the report of the Expert Meeting. The difference between the Canadian proposed model and the one proposed in the Expert Meeting report is a high-level aggregation of food consumption data (e.g. one consumption factor for total muscle consumption, as opposed to beef muscle + pork muscle + chicken muscle etc.) to avoid additive estimation between species. This approach simplifies the exposure assessment, especially when done iteratively for establishing withdrawal periods. However, Canada acknowledges that there might be situations where exposure assessment at the individual animal species level would be required or preferred, using specific data at a much lower level of segregation (e.g. a product that will never be developed for use in more than one food-producing animal species). Hence, the data in Table 4 of the Expert Meeting report may have to be used in those specific situations.

Chronic exposure assessment

A simplified food basket system for chronic exposure is proposed in Table A7-1. A detailed description of how these values were derived is presented in Appendix 1.

Table A7-1. Simplified food consumption factors proposed for use in chronic exposure assessment (modified based on the data and method proposed by the Expert Meeting)

	General population (60 kg)		Children (2–6 years) (15 kg)		
Food type	Mean total population (g/person per day)	High-level chronic consumer (g/person per day)	Mean total population (g/person per day)	High-level chronic consumer (g/person per day)	Infants (5 kg) (g/person per day)
Muscle[a]	300	425	100	200	—
Liver	15	250	—	—	—
Kidney	10	200	—	—	—
Other offal[b]	25	250	2	110	—
Fat[c]	75	75	10	30	—
Eggs	75	150	30	115	—
Milk	400	1050	600	1050	750
Honey	5	50	2	20	—

[a] For fish, muscle and skin in natural proportion.
[b] When unconventional offal tissues are to be included in the exposure assessment, 25 g mean consumption and 250 g high-level consumption for adults and 2 g mean consumption and 110 g high-level consumption for children to be divided between conventional (liver and kidney) and unconventional (e.g. lungs) offal tissues.
[c] For swine and poultry, skin and fat.

The simplified model was tested using the examples and data used by the Expert Meeting. The simplified model slightly overestimates the exposure compared with the model proposed in the Expert Meeting report. For example, using the simplified model and the data provided in Table 5 of the report, the exposure estimate for triclabendazole residues from cattle tissue would be 95.3 µg/person per day (72.4 + 19.6 + 0.9 + 2.4) and that from sheep tissue would be 33 µg/person per day. These represented 53% and 33% of the ADI, respectively. The

estimation from the experts' proposed model represented 46% of the ADI, but could increase if a new animal species is added to the label claim. However, in the simplified model, as the exposure is assessed for each species separately, adding a label claim subsequently will have no impact on exposure assessment, as well as on the withdrawal period or the MRLs.

The advantages of the proposed simplified approach are as follows:

1. The simplified model meets the specific requests made by CCRVDF to JECFA:
   a. It uses the current international food consumption data.
   b. It provides a simple model (similar to the existing JECFA food basket) for exposure assessment.
   c. It proposes approaches for acute and chronic exposure assessment.
   d. It provides simplicity for including non-standard tissues (e.g. lungs) in the exposure assessment. For example, as, per the data reviewed, mean total offal consumption is 25 g and a habitual heavy consumer could consume a maximum of 250 g of standard (e.g. liver) or non-standard offal (e.g. lungs), this model could assess total exposure from both standard (i.e. muscle, liver, kidney and fat) as well as non-standard (e.g. lungs) tissue consumption.
2. The simplified model also addresses stakeholders' major concerns:
   a. It provides a simplified method that could be harmonized across nations.
   b. It simplifies the approach, thereby avoiding a potential requirement for additional data for exposure assessment (especially by the national authority) each time a new species is added to the label claim.
3. The simplified method can be easily adopted by national regulators. Although JECFA does not establish withdrawal periods or set the use conditions of a veterinary drug, national authorities do this in conjunction with the establishment of MRLs. A simple and practical approach that can be used not only by JECFA but also by national regulators (including developing countries) would facilitate harmonization of data requirements and MRL/withdrawal period setting and would also simplify public safety assessment and facilitate international trade. By removing the additive approach, the simplified model eliminates the need to reassess exposure every time a new species is added to the label, thereby greatly facilitating its adoption by national regulators.
4. The exposure assessment becomes independent of the number of species for which the drug is approved—i.e. exposure assessment is conducted for each species separately (similar to existing JECFA practice).
5. The exposure estimates derived from this approach would be supportive of JECFA's traditional way of expressing ADI as a range (e.g. 0–50 µg/kg body weight) and factoring in the good veterinary practice philosophy in the safety assessment of veterinary drug residues.
6. This method could still retain the flexibility of using the species-specific consumption data in exposure assessment for special circumstances (e.g. drug would be used only in one species, or species-specific exposure assessment would be required for establishing withdrawal period to meet good agricultural practice).

Acute exposure assessment

For acute exposure assessment, it could be assumed that a person consuming a very large quantity of one type of meat or eggs would not also consume a large quantity of another meat or eggs. So, the proposed acute exposure assessment is not an additive model. As a result, the acute exposure assessment would be specific to each species for which the drug is assessed.

However, the acute exposure model could also benefit from some simplification. For example, the highest muscle consumption value recommended for acute exposure assessment (see Table 3 of the Expert Meeting report) is 419–665 g/person per day. A possible simplification would be to specify, for example, 600 g as the consumption value of mammalian (or all) muscle to be used in exposure assessment. Similar values for all commodities could also be identified.

One additional point that might need consideration for acute exposure assessment is whether some heavy consumers of meat (muscle, liver, kidney, fat or eggs) could also consume a high quantity of milk on the same day. If so, exposure estimates from tissues and milk might have to be added to compare with the ARfD.

Appendix 1: Simplified food consumption factors proposed for use in chronic exposure assessment, with explanation

	General population		Children (2–6 years)		
Food type	Mean total population[a] (g/person per day)	High-level chronic consumer[b] (g/person per day)	Mean total population[a] (g/person per day)	High-level chronic consumer[b] (g/person per day)	Infants (g/person per day)
Muscle[c]	300[d]	425[e]	100[f]	200[g]	—
Liver	15[h]	250[i]	—		—
Kidney	10[i]	200[i]	—		—
Other offal[j]	—[i]	250	2	110	—
Fat	75[k]	75[l]	10[m]	30[n]	—
Eggs	75[o]	150	30[p]	115	—
Milk	400[q]	1050[r]	600[q]	1050[r]	750
Honey	5	50[s]	2	20[s]	—

[a] For the mean total population consumption, mammalian, poultry and seafood consumption data were added.
[b] For high-level chronic consumption, it was assumed that only one type of tissue will be consumed in a high quantity in a day. Hence, the highest reported value for mammalian tissue, poultry or seafood will be used.
[c] Muscle for mammals and poultry, muscle and skin in natural proportion for fish.
[d] The sum of all mammalian muscle (158 g), poultry muscle (131 g) and all seafood (80 g) would be 369 g, rounded down to 300 g. This rounding down is justified because the mean consumption presented in Table 4 of the Expert Meeting report is considered to significantly overestimate the mean consumption (see comment 1d above).
[e] The highest high-level chronic consumption of 428 g for pork rounded to 425 g.
[f] The sum of all mammalian muscle (57 g), poultry muscle (37 g) and seafood (40 g) of 134 g rounded to 100 g (see comment 1d above for rounding down justification).
[g] The highest high-level consumption for poultry muscle of 207 g rounded to 200 g.
[h] All mammalian offal of 14 g and all poultry offal of 10 g, distributed to liver 14 g (rounded to 15) and kidney (10 g). Considering relatively higher weight of liver in animals, and hence increased likelihood of eating liver as part of offal, higher value assigned to liver. As the value divided for liver and kidney was for total offal, when exposure assessment is to be expanded to other non-conventional offal tissues, the same 25 g total offal values should be divided between liver, kidney and other offal (e.g. lungs).
[i] The figure for mammalian liver and kidney used.
[j] Only to be used when data for liver and kidney are not available or when other non-conventional offal tissues are to be assessed together with liver and kidneys. When non-conventional offal tissues are to be assessed, reported consumption value to be divided between liver, kidney and other non-conventional tissues.
[k] The sum of mammalian trimmed fat, skin and added fat (37 g) and poultry fat and skin (37 g) rounded to 75 g. This value would represent fat (for most species), but skin and fat for swine and poultry.
[l] The highest mammalian fat (53 g) and poultry skin/fat (43 g) consumed is 53 g, which is lower than mean consumption of 75 g. Hence, the high-level consumption value increased to bring it up to mean consumption level.
[m] Rounded from the reported figure of 9 g.
[n] The highest high-level consumption value for mammalian (30 g) fat used.
[o] Rounded to 75 g from 71 g reported.
[p] Rounded to 30 g from 28 g reported.
[q] Rounded to 400 g from 378 g for adults and to 600 g from 634 g for children.
[r] Rounded to 1050 g from 1057 g for adults and 1065 g for children.
[s] The figure proposed by the seventieth meeting of JECFA based on more robust survey data (26 000 portion data from 9000 honey eaters) is recommended for use.

Joint FAO/WHO Expert Meeting on Dietary

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