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[1] Text with EEA relevance.

EN

Acts whose titles are printed in light type are those relating to day-to-day management of agricultural matters, and are generally valid for a limited period.

The titles of all other acts are printed in bold type and preceded by an asterisk.

II

(Non-legislative acts)

REGULATIONS

COMMISSION REGULATION (EU) 2018/781

of 29 May 2018

amending Regulation (EC) No 847/2000 as regards the definition of the concept 'similar medicinal product'

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products ([1]), and in particular Article 8(4) thereof,

Whereas:

(1) Regulation (EC) No 141/2000 was adopted to promote research in the field of rare diseases. It offers undertakings that develop orphan medicinal products the prospect of obtaining market exclusivity for a certain number of years.

(2) Commission Regulation (EC) No 847/2000 ([2]) provides a definition of the concept 'similar medicinal product', which includes specific cases defining what kind of products are to be regarded as similar for the purposes of the application of Article 8 of Regulation (EC) No 141/2000. That definition should be updated in the light of new scientific and technical knowledge, in particular, due to major developments in the field of biological medicines, and especially advanced therapy medicinal products, and in the light of experience gained with regard to the designation and regulation of orphan medicinal products.

(3) In addition, there is a need for a clear definition of the concept 'principal molecular structural features', which is used within the definition of the concept 'similar active substance', which is in turn used within the definition of the concept 'similar medicinal product'. As regards the biological medicinal products, the definition of 'principal molecular structural features' shall capture certain molecular modifications significantly contributing to the functional characteristics of the active substance that would impact whether or not the products are considered as similar. However, for advanced therapy medicinal products the principal molecular structural features cannot be fully identified. Therefore, in the case of advanced therapy medicinal products the similarity between two active substances should be assessed on the basis of the biological and functional characteristics.

(4) The definition of 'active substance' should be deleted as Article 8(4) of Regulation (EC) No 141/2000 does not empower the Commission to define the term 'active substance'. The term 'active substance' is legally defined in Article 1(3)(a) of Directive 2001/83/EC of the European Parliament and of the Council ([3]) and the scope and purpose of Article 3(3) of Regulation (EC) No 847/2000 are related to the definitions of the concepts 'similar medicinal product' and 'clinical superiority'.

([1]) OJ L 18, 22.1.2000, p. 1.
([2]) Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority' (OJ L 103, 28.4.2000, p. 5).
([3]) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

(5) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use,

HAS ADOPTED THIS REGULATION:

Article 1

In Article 3(3) of Regulation (EC) No 847/2000, the introductory sentence and points (a), (b) and (c) are replaced by the following:

'For the purposes of the application of Article 8 of Regulation (EC) No 141/2000 on orphan medicinal products, the following definitions shall apply:

(a) deleted;

(b) "similar medicinal product" means a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication;

(c) "similar active substance" means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism. However, in the case of advanced therapy medicinal products, for which the principal molecular structural features cannot be fully defined, the similarity between two active substances shall be assessed on the basis of the biological and functional characteristics.

For the purpose of application of point (c) above, the following applies for:

(1) Chemical medicinal products

The principal molecular structural features are the relevant structural components of an active substance. They can be the whole or part of the molecule. Whether the principal molecular structural features are the same between two or more molecules will be identified by comparison of their structures.

(1.1) Isomers, mixture of isomers, complexes, esters, ethers, salts, and derivatives of the original active substance, or an active substance that differs from the original active substance only with respect to minor changes in the molecular structure, such as a structural analogue, shall be considered similar.

(1.2) Synthetic polynucleotide substances, single or double stranded, consisting of two or more distinct nucleotides where:

— the difference in the nucleotide sequence of the purine and pyrimidine bases or their derivatives is not major, shall be considered similar. Therefore for antisense or interfering nucleotide substances, addition, substitution or deletion of a nucleotide not significantly affecting the kinetics of hybridisation to the target shall normally be considered similar,

— the difference in structure related to modifications of the ribose or deoxyribose backbone sugars or to the replacement of the backbone sugars by synthetic analogues shall normally result in substances being considered similar. For antisense or interfering nucleotide substances, changes in the (deoxy-)ribose not significantly affecting the kinetics of hybridisation to the target would normally be considered similar.

(2) Biological medicinal products (other than advanced therapy medicinal products)

The principal molecular structural features are the structural components of an active substance that are relevant for the functional characteristics of that substance. The principal molecular structural features may be composed of a therapeutic moiety or a therapeutic moiety in combination with an additional structural element(s) significantly contributing to the functional characteristics of the active substance.

Such an additional structural element(s) can be conjugated, fused or linked by other means to the therapeutic moiety or can be an extension of the therapeutic moiety protein backbone by additional amino acids. Substances with structural elements for which similar methods of modification or conjugation technology are used shall normally result in similar substances.

Biological active substances that differ from the original biological substance only with respect to minor changes in the molecular structure shall be considered similar.

(2.1) Proteinaceous substances:

If the difference in structure between them is due to post-translational events (such as different glycosylation patterns) substances shall normally be considered similar. However, exceptionally some post-translational modifications may result in a non-similar substance, if there is significant effect on the functional characteristics of the substance.

If the difference in the amino acid sequence is not major, substances shall normally be considered similar. Therefore, two pharmacologically related protein substances of the same group (for example, having differences related to e.g. N-terminal methionine, naturally extracted versus rDNA-derived proteins or other minor variants) shall normally be considered similar. However, the addition of a structural element may result in substances being considered non-similar if this significantly affects the functional characteristics of the substance.

Monoclonal antibodies binding to the same target epitope shall normally be considered similar. However, two monoclonal antibody conjugates or fusion proteins could be determined to be non-similar if either the Complementary Determining Region sequences of the antibody or the additional structural element of the conjugated monoclonal antibody were different.

(2.2) Polysaccharide substances:

If the substances have identical saccharide repeating units, even if the number of units varies, they shall normally be considered similar.

A conjugated polysaccharide vaccine compared to a non-conjugated polysaccharide vaccine containing the same antigen is considered a non-similar substance.

(3) Advanced Therapy Medicinal Products (ATMPs)

(3.1) Cell-based ATMPs: Two related cell-based medicinal products are not similar if:

— there are differences in starting materials or the final composition of the product which have significant impact on the biological characteristics and/or biological activity relevant for the intended therapeutic effect and/or safety attributes of the product. The different source of the starting materials (e.g. as in the case of autologous ATMPs) is not sufficient to support a claim that two products are non-similar, or

— there are differences in the manufacturing technology having a significant impact on the biological characteristics and/or biological activity relevant for the intended therapeutic effect and/or safety attributes of the product.

(3.2) Gene therapy medicinal products: Two gene therapy medicinal products shall not be considered similar when there are differences in the therapeutic sequence, viral vector, transfer system, regulatory sequences or manufacturing technology that significantly affect the biological characteristics and/or biological activity relevant for the intended therapeutic effect and/or safety attributes of the product.

Differences in the therapeutic sequence without a significant impact on the intended therapeutic effect are not sufficient to support the claim that two gene therapy medicinal products are non-similar.

(3.3) Genetically modified cells. The considerations under (3.1) and (3.2) apply.

(4) Radiopharmaceutical medicinal products

The same radiopharmaceutical active substance, or one differing from the original in radionuclide, ligand, site of labelling or molecule-radionuclide coupling mechanism linking the molecule and radionuclide provided that it acts via the same mechanism shall be considered similar substances.'

Article 2

Entry into force and application

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 29 May 2018.

For the Commission
The President
Jean-Claude JUNCKER

COMMISSION REGULATION (EU) 2018/782

of 29 May 2018

establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council ([1]), and in particular Article 13(2)(a) thereof,

Whereas:

(1) Regulation (EC) No 470/2009 provides that, except in cases where the Codex Alimentarius procedure applies, any pharmacologically active substance intended for use in the Union in veterinary medicinal products which are to be administered to food-producing animals shall be subject to an opinion of the European Medicines Agency ('Agency') on the maximum residue limits ('MRLs') of pharmacologically active substances used or intended to be used in veterinary medicinal products. The Agency's opinion should consist of a scientific risk assessment and risk management recommendations.

(2) Regulation (EC) No 470/2009 empowers the Commission to adopt measures establishing the methodological principles for the risk assessment and risk management recommendations regarding the establishment of the MRLs of pharmacologically active substances.

(3) In order to provide legal certainty, clarity and predictability with regard to the process of the establishment of MRLs, it is appropriate that the criteria against which the Agency appraise the applications are provided for in this Regulation.

(4) The methodological principles for the risk assessment and risk management recommendations should aim to ensure a high level of human health protection, whilst also ensuring that human health, animal health and animal welfare are not negatively affected by the lack of availability of appropriate veterinary medicinal products.

(5) Taking into account the requirements set out in Article 6 of Regulation (EC) No 470/2009, the detailed rules on the methodological principles for the scientific risk assessment part of the Agency's opinion should be laid down in this Regulation.

(6) Taking into account the requirements set out in Article 7 of Regulation (EC) No 470/2009, the detailed rules on the methodological principles for the risk management recommendations part of Agency's opinion should be laid down in this Regulation. In the risk management recommendations, the Agency is also required to consider the availability of alternative substances and other legitimate factors, such as the technological aspects of food and feed production or the feasibility of controls. Therefore it is appropriate to lay down rules on that requirement.

(7) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Veterinary Medicinal Products,

HAS ADOPTED THIS REGULATION:

Article 1

Subject matter

1. This Regulation sets out the methodological principles for the scientific risk assessment and risk management recommendations referred to in Articles 6 and 7 of Regulation (EC) No 470/2009 that shall be applied by the Agency when preparing opinions on the MRLs of pharmacologically active substances which may be permitted in food of animal origin under that Regulation.

([1]) OJ L 152, 16.6.2009, p. 11.

2. The methodological principles for the scientific risk assessment are set out in Annex I.

3. The methodological principles for the risk management recommendations are set out in Annex II.

Article 2

Definitions

For the purposes of this Regulation, in addition to the definitions set out in Regulation (EC) No 470/2009, the following definitions shall apply:

— 'major metabolites' means metabolites comprising ≥ 100 μg/kg or ≥ 10 % of the total residue in a sample collected from the target animal species in the metabolism study,

— 'marker residue' means a residue whose concentration is in a known relationship to the concentration of total residue in an edible tissue,

— 'dairy starter cultures' means prepared cultures of microorganism employed in the manufacture of a variety of dairy products including butter, cheese, yoghurt and cultured milk.

Article 3

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 29 May 2018.

For the Commission
The President
Jean-Claude JUNCKER

ANNEX I

Methodological principles for the scientific risk assessment referred to in Article 6 of Regulation (EC) No 470/2009

I. GENERAL PRINCIPLES

I.1. Safety and residue tests for the establishment of maximum residue limits ('MRLs') shall be carried out in conformity with the provisions related to Good Laboratory Practice ('GLP') as laid down in Directive 2004/10/EC of the European Parliament and of the Council. ([1])

If data are available that have not been generated under GLP conditions, the potential impact of this shall be addressed.

I.2. Use of experimental animals in safety and residue tests shall comply with Directive 2010/63/EU of the European Parliament and of the Council ([2]).

I.3. Documentation presented in relation to safety and residue tests shall name the laboratory where the work was performed and shall be signed and dated. Summaries of any studies that are not accompanied by the raw data shall not be accepted as valid documentation.

Design, methods and conduct of the studies, name and qualifications of investigator, place and period of time during which the study was undertaken shall be clear from the test reports. The experimental techniques shall be described in such detail as to allow them to be reproduced, and the investigator shall establish their validity. All abbreviations and codes, irrespective of whether they are internationally accepted or not, shall be accompanied by a key.

I.4. Where applicable, all observed results from the studies submitted shall be evaluated by an appropriate statistical method and be discussed in conjunction with the other available studies. The results of all studies shall be presented in a form that facilitates their review.

I.5. Test reports shall include the following information (where applicable):

(a) chemical identification of the test pharmacologically active substance, including the isomer ratio and the enantiomers, if appropriate;

(b) purity of the test substance;

(c) formulation of the administered drug and method of dose preparation;

(d) stability, including stability in vehicle and feed when so administered;

(e) mode of dose administration (dose (expressed in mg/kg body weight), frequency of dosing, and duration of treatment);

(f) for administration of the test substance other than in the diet or drinking water: the characteristics of the vehicle, including toxicological characteristics;

(g) species, strain and source of test animals used, use of specific pathogen free animals, sex of the dosed animals, age of the animals at the beginning of the dosing, number of dosed animals;

(h) dose levels and route and frequency of administration (with dosage in mg/kg bodyweight/day), test period, parameters followed, frequency of observation; conditions of animal husbandry including environmental conditions, water and food consumption (especially for drugs administered in drinking water and/or feed);

(i) sampling time points;

(j) description of toxic signs with the inclusion of time of onset, degree and duration (for safety tests), where appropriate;

([1]) Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (OJ L 50, 20.2.2004, p. 44).

([2]) Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, p. 33).

(k) results of the clinical observations, gross necropsy, histopathology and of all other parameters investigated (for safety tests), where appropriate;

(l) where appropriate, an estimate of a no observed (adverse) effect level ('NO(A)EL') or lowest observed (adverse) effect level ('LO(A)EL') or lower bound of the benchmark dose ('BMDL') (for safety tests);

(m) weight of dosed animals;

(n) milk and egg production (if applicable);

(o) specific activity and radio-purity of labelled substances (for residues tests);

(p) sample collection, sample size, and sample storage;

(q) analytical methods: a complete description of the procedure, including preparation of analytical samples, instrumentation and data derived from standards, control tissues, fortified tissues and tissues with incurred residues; validation data for the analytical method shall be provided, including limit of detection, limit of quantification, linearity in and around the relevant range of concentrations, stability, accuracy, precision and susceptibility to interferences;

(r) raw data of all test results including those of the analytical method used to determine the residues in the edible tissues or products, methods of calculation.

I.6. Biological substances other than those identified in Article 1(2)(a) of Regulation (EC) No 470/2009 of the European Parliament and of the Council [1] shall be:

(a) subject to a normal MRL where the biological substance is chemical-like insofar as it could be produced by chemical synthesis and so presents similar concerns to chemical substances and can be expected to leave residues in the same way as chemical substances (e.g. cytokines, hormones);

(b) evaluated on a case-by-case basis where the biological substance is chemical-unlike insofar as being more complex than chemically synthesised pharmacologically active substances and so may contain multiple chemical types whose residues may generally be cells, amino acids, lipids, carbohydrates, nucleic acids and their breakdown products.

I.7. For chemical-unlike biological substances, a report describing the scientific basis for the request on whether a full MRL evaluation is required or not shall be required together with the following information:

(a) the nature of the biological substance (e.g. cell, tissue, live or killed organism) and a comparison with similar biological substances to which consumers are known to be routinely exposed;

(b) a description of the mechanism of action underlying the substances therapeutic effect and, if available, information on its potency;

(c) the fate of the substance in the treated animal (i.e. is it bioavailable, are residues expected in food commodities);

(d) any activity that the substance may have in the human gut (are the residues inactive or do they produce local effects);

(e) the systemic availability of residues following ingestion of residues by consumers, along with a worst case consumer exposure estimate.

The information provided above shall be evaluated in accordance with the guidance published by the European Medicines Agency ('Agency') in order to determine whether there is the need for a MRL evaluation. Biological substances for which it is concluded that a MRL evaluation is not required shall be published by the Agency in a list of such substances.

[1] Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council (OJ L 152, 16.6.2009, p. 11).

I.8. Certain aspects of the data to be submitted in support of a MRL application for a substance for use in minor species or for minor uses may be reduced in comparison to the requirements for a substance that does not fall into this category. Evaluation shall be made based on the data requirements laid out in the Agency's *'Guideline on safety and residue data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market'* ([1]).

I.9. The general principles for the derivation of MRLs for biocidal substances used in animal husbandry laid down in Article 10 of Regulation (EC) No 470/2009 shall be the same as for veterinary medicinal products.

II. SAFETY FILE

II.1. A full safety data package as described in this section shall be required for MRL evaluation for substances that have not previously been used in food-producing species.

II.2. Where relevant and high quality literature data where all the details of the study are described are available, it may be possible to rely on these in place of a full study report commissioned by the applicant.

II.3. If data are not provided for standard endpoints, thorough justification shall be required.

II.4. **Detailed and critical summary**

II.4.1. A detailed and critical summary of the safety file shall be required.

II.4.2. The detailed and critical summary shall:

(a) include a clear position on the adequacy of the data presented, in light of current scientific knowledge;

(b) have an introduction describing the actual or proposed pattern of use of the substance under review in animal husbandry and a summary of any other experience of its use;

(c) consider the extent to which the substance concerned has similarities to other known substances, which may be relevant for the evaluation;

(d) cover all standard data requirements, as set out in the Commission Implementing Regulation (EU) 2017/12 ([2]), provide a critical evaluation of the available experimental studies and an interpretation of the results;

(e) provide scientific justification for the omission of any studies that are described in this section;

(f) discuss requirements for additional studies;

(g) provide a description and explanation of the key findings for each study. The following issues shall be discussed: the animal species used, the number(s) of animals used, the route(s) of administration, the dosage(s), the duration of treatment, the exposure achieved, the dose response relationship, the nature of the adverse effects (their onset and duration, their dose dependency and reversibility and any species related or sex-related differences), known relevant structure-activity relationships and relevance of the findings for human consumers;

(h) give a justification for the NO(A)EL or LO(A)EL or BMDL proposed for each study;

(i) summarise and discuss relevant scientific literature, including reports of evaluations undertaken by other scientific bodies (such as the European Food Safety Authority ('EFSA'), European Chemicals Agency ('ECHA') and the Joint Food and Agriculture Organisation ('FAO')/World Health Organisation ('WHO') Expert Committee on Food Additives ('JECFA')). If detailed references to published scientific literature are used, all the requirements set out under point I.5 shall be met, as far as possible;

([1]) Safety and residue data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001536.jsp&mid=WC0b01ac058002dd38).

([2]) Commission Implementing Regulation (EU) 2017/12 of 6 January 2017 regarding the form and content of the applications and requests for the establishment of maximum residue limits in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council (OJ L 4, 7.1.2017, p. 1).

(j) include information on the quality of batches of test substances used in the safety studies. Any association between findings and the quality of the test substances and/or the medicinal products shall be indicated. When necessary, a critical evaluation of the impurities present in the active ingredient shall be presented and information on their potential biological effects shall be given. The implications of any differences of the chirality, chemical form and impurity profile between the substance used in the safety studies and the form to be marketed shall be discussed;

(k) discuss the GLP status of the studies submitted;

(l) discuss possible deficiencies in the design and conduct of the studies and their documentation, making reference to published Agency and other guidance. Any deviations from applicable guidance shall be highlighted and the impact of the deviation discussed and scientifically justified;

(m) comment on the use of experimental animals in the studies and whether the studies were conducted in accordance with Directive 2010/63/EU;

(n) provide a justification for the selection of critical NO(A)EL(s) or BMDL(s) and the derivation of the acceptable daily intake ('ADI'), justifying the selection of uncertainty factors. If no ADI is proposed, or if an alternative toxicological reference value is selected, this shall be thoroughly justified.

II.4.3. Annexes to the detailed and critical summary shall include:

(a) list of references — a list of all references shall be provided in accordance with internationally accepted standards. The references themselves shall be included in the dossier;

(b) tabulated study reports — tabular summaries of study reports. In addition, a complete set of study reports shall be included in the dossier.

II.5. **Precise identification of the substance concerned by the application**

II.5.1. The data shall demonstrate that the substance has been precisely identified and characterised in order to ensure that the substance used in safety studies is reflective of the substance to be used in the field.

II.5.2. Batches used in safety studies shall be identified and adequate specifications shall be provided, including purity (concentrations of impurities), isomer ratios and enantiomers, solubility and any other factor that may influence its activity.

II.5.3. Information on the chemical and physicochemical properties of the substance may allow concerns to be identified and/or addressed based on known properties of substances with similar chemical and physico-chemical properties.

II.6. **Pharmacology**

II.6.1. *Pharmacodynamics*

II.6.1.1. Data from the pharmacodynamic studies shall aim to enable the identification and characterisation of the mode/mechanisms of action that underlie the intended therapeutic effects as well as those underlying adverse effects/side effects. These studies shall be designed on a case-by-case basis taking account of available information with regard to the likely pharmacological actions for the substance.

II.6.1.2. Particular consideration shall be given in relation to pharmacodynamic effects of the substance that may occur at doses below those required to produce toxicological effects, with consideration given to the need for derivation of a pharmacological ADI.

II.6.1.3. Studies relevant to the establishment of a pharmacological ADI shall identify or characterise the mode of action, the dose-response relationship and identify a NOEL or BMDL, where possible and shall be used as a starting point from which a pharmacological ADI is derived. Where appropriate data are available from studies in humans (e.g. for substances with a history of use in human medicine) these shall usually be the most useful in identifying a pharmacological NOEL or BMDL. Guidance published by the Agency on the establishment of pharmacological ADI [1] shall be followed.

[1] Approach to establish a pharmacological acceptable daily intake (ADI) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001530.jsp&mid=).

II.6.1.4. Data on the pharmacodynamic effects of a substance shall:

(a) enable to identify/characterise the mode/mechanism of action of the substance;

(b) enable characterisation of the dose-response relationship for relevant pharmacological endpoints;

(c) provide insight into the potential toxic effects of the substance based on knowledge of known effects of other substances with similar pharmacodynamic properties;

(d) aid the understanding of the mechanisms underlying adverse effects seen in toxicology studies;

(e) provide, in certain cases, information on the relevance of effects seen in laboratory animals for humans.

II.6.1.5. If pharmacodynamic data are not provided, their absence shall be scientifically justified and the impact of their absence discussed.

II.6.1.6. If a pharmacological ADI is not derived, its absence shall be scientifically justified.

II.6.2. *Pharmacokinetics*

II.6.2.1. Pharmacokinetic investigations shall provide information on the absorption of the substance, its distribution and persistence in the tissues, its metabolism and excretion. The oral route shall be the main route of administration in the pharmacokinetic studies as this is the route by which consumers are exposed.

II.6.2.2. Metabolites produced in the laboratory animal species shall be compared to those seen in the target animal species, in line with the guidance provided in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products ('VICH') — *VICH GL47: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: laboratory animal comparative metabolism studies* ([1]).

II.6.2.3. The pharmacokinetic data obtained from studies in laboratory animals shall be used to model the fate of the substance ingested by humans.

II.6.2.4. Pharmacokinetic data in laboratory animals shall also be used to determine whether the metabolites that consumers will ingest in animal-derived food commodities are also produced in the laboratory animals used for safety testing. This is necessary in order to determine the relevance of the toxicological effects and NO(A)ELs or BMDLs obtained in the toxicology studies. If the laboratory animals produce the same metabolites to those produced by the food-producing animal, the laboratory animals shall be considered to have been auto-exposed to the metabolites that humans would consume. This is ordinarily taken as evidence that the safety of metabolites has been adequately assessed in the toxicology studies. If the metabolites produced by the target animal species are not produced in the laboratory animal studies, there may be a need to conduct safety studies using the major metabolite(s) produced in the target animal.

II.6.2.5. Pharmacokinetic data may also help to explain unusual results obtained in toxicity studies, such as an apparent lack of dose-response when the drug is not well absorbed.

II.6.3. *Toxicology*

II.6.3.1. General principles

II.6.3.1.1. Animal studies shall be performed by the oral route since this is the route of exposure for the consumer.

II.6.3.1.2. Animal studies shall be conducted in established strains of laboratory animals for which historical data are available. Each substance shall be tested in the species and strain of animals that is the best model for its effects in humans.

([1]) VICH GL47 Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: laboratory animal comparative metabolism studies (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001515.jsp&mid=WC0b01ac058002dd37).

II.6.3.1.3. The substance to be tested shall be the active substance. However, if residues in foods derived from treated animals include significant amounts of a metabolite which is not produced in the laboratory animal species, the toxicity of the metabolite may need to be assessed separately.

II.6.3.1.4. *VICH GL33: Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to testing* ([1]) shall be followed.

II.6.3.2. Single-dose toxicity, if available

II.6.3.2.1. Acute toxicity studies may have been performed for reasons other than the evaluation of consumer safety (e.g. for the evaluation of the user safety of a product) or may have been reported in published literature. Reports of any such studies shall be submitted as part of the Safety File.

II.6.3.2.2. If available, acute toxicity data which may contribute to the overall picture of the toxicological profile of the substance and may highlight effects to look out for in longer term studies shall be provided.

II.6.3.3. Repeat dose toxicity

II.6.3.3.1. *Repeat dose (90 day) oral toxicity testing*

II.6.3.3.1.1. Data from repeat dose (90 day) oral toxicity studies shall be provided for both a rodent and a non-rodent species, together with the reasons for the choice of species, considering any available knowledge of the metabolism of the substance in animals and humans.

II.6.3.3.1.2. Data from repeat dose oral toxicity testing studies shall:

(a) allow the evaluation of the functional and morphological changes due to repeated administration of the test substance(s) and how these changes are related to dose;

(b) allow the establishment of a NO(A)EL or LO(A)EL or BMDL;

(c) inform the choice of dose levels for chronic studies as well as the choice of the most appropriate species for chronic studies.

II.6.3.3.1.3. Guidance on the design of repeat dose (90-day) studies is provided in *VICH GL31: Studies to evaluate the safety of residues of veterinary drugs in human food: repeat-dose (90 days) toxicity testing* ([2]) and shall be followed. Any departures from established guidance shall be justified and the impact discussed.

II.6.3.3.1.4. The absence of repeat dose (90-day) oral toxicity studies in rodents and/or non-rodents shall also be scientifically justified and the impact of their absence discussed.

II.6.3.3.2. *Repeat-dose (chronic) toxicity testing*

II.6.3.3.2.1. Chronic toxicity testing shall be conducted in at least one species. This shall be the most appropriate species chosen on the basis of all available scientific data, including the results of the 90-day studies, with the default species being the rat.

II.6.3.3.2.2. The data from chronic oral toxicity testing studies shall allow:

(a) the evaluation of the functional and morphological changes due to repeated administration of the test substance(s) and how these changes are related to dose;

(b) the establishment of a NO(A)EL or LO(A)EL or BMDL.

([1]) VICH GL33 Safety studies for veterinary drug residues in human food: general approach to testing (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001480.jsp&mid=WC0b01ac058002dd37).

([2]) VICH GL31 Safety studies for veterinary drug residues in human food: repeat-dose (90) toxicity testing (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001478.jsp&mid=WC0b01ac058002dd37).

II.6.3.3.2.3. Guidance on the design of repeat dose (chronic) studies is provided in *VICH GL37: Studies to evaluate the safety of residues of veterinary drugs in human food: repeat-dose (chronic) toxicity testing* ([1]) and shall be followed. Any departures from established guidance shall be justified and the impact discussed.

II.6.3.3.2.4. If a repeat dose (chronic) oral toxicity study is not provided, its absence shall be scientifically justified and the impact of its absence discussed.

II.6.3.4. Tolerance in target species, if available

II.6.3.4.1. Data on tolerance in target species shall not be required for the evaluation of consumer safety. However, where relevant data have been generated or are reported in published literature, these shall be submitted as part of the Safety File.

II.6.3.4.2. If available, data on tolerance in target species may contribute to the overall picture of the toxicological profile of the substance and may highlight effects to look out for in toxicity studies.

II.6.3.5. Reproductive toxicity, including developmental toxicity

II.6.3.5.1. *Study of the effects on reproduction*

II.6.3.5.1.1. General reproductive toxicity testing shall be conducted in at least one species, the default species being the rat. The oral route of administration shall be used.

II.6.3.5.1.2. Tests for effects on reproduction shall aim to identify and characterise adverse effects of the test substance on reproductive performance of exposed adults as well as on the normal development of their progeny.

II.6.3.5.1.3. Tests shall identify potential effects on male and female reproductive performance, such as gonadal function, oestrus cycle, mating behaviour, conception, parturition, lactation, weaning and on the growth and development of the offspring. These studies may also provide information about adverse developmental effects such as teratogenesis.

II.6.3.5.1.4. If evidence suggests the occurrence of effects on development of the central nervous system, specific investigations of such effects may be required, for example through evaluation of results of other tests (see Section II.6.4.1).

II.6.3.5.1.5. The data shall allow the establishment of a NO(A)EL or LO(A)EL or BMDL.

II.6.3.5.1.6. Guidance on the design of reproduction toxicity testing studies is provided in *VICH GL22: Studies to evaluate the safety of residues of veterinary drugs in human food: reproduction testing* ([2]) and shall be followed. Any departures from established guidance shall be justified and the impact discussed.

II.6.3.5.1.7. If a reproduction toxicity study is not provided, its absence shall be scientifically justified and the impact of its absence discussed.

II.6.3.5.2. *Study of developmental toxicity*

II.6.3.5.2.1. The aim of developmental toxicity studies shall be to detect any adverse effects on the pregnant female and the development of the embryo and foetus as a result of exposure from implantation through the entire gestation period. Such effects may include enhanced toxicity in the pregnant females, embryo foetal death, altered foetal growth and structural abnormalities and anomalies in the foetus.

II.6.3.5.2.2. If clear evidence of teratogenicity is seen in the rat, a study in a second species shall not be necessary except where a review of all the core studies indicates that the ADI would be based on the rat teratogenicity study. Testing in a second species (normally rabbit) is expected if no evidence of teratogenicity or equivocal results were seen in the rat.

([1]) VICH GL37 Safety of veterinary drugs in human food repeat-dose (chronic) toxicity testing (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001481.jsp&mid=WC0b01ac058002dd37).

([2]) VICH GL22 Safety studies for veterinary drug residues in human food: reproduction studies (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001475.jsp&mid=WC0b01ac058002dd37).

II.6.3.5.2.3. Guidance on the approach towards developmental toxicity testing is described in *VICH GL32: Studies to evaluate the safety of residues of veterinary drugs in human food: developmental toxicity testing* ([1]). This provides for a tiered approach, with testing to be undertaken initially in a single species (rat). Any departures from established guidance shall be justified and the impact discussed.

II.6.3.5.2.4. Studies shall use the oral route of administration.

II.6.3.5.2.5. The data shall allow the establishment of a NO(A)EL or LO(A)EL or BMDL.

II.6.3.5.2.6. If a developmental toxicity study is not provided, its absence shall be scientifically justified and the impact of its absence discussed.

II.6.3.6. Genotoxicity

II.6.3.6.1. In most cases the substance to be tested shall be the parent compound only. However, in some cases there may be a need to test in addition one or more of the major metabolites separately. This would be the case if a major metabolite produced in the target species is not produced in the laboratory animal species.

II.6.3.6.2. *VICH GL23: Studies to evaluate the safety of residues of veterinary drugs in human food: genotoxicity testing* ([2]) identifies a standard battery of tests recommended for addressing the genotoxic potential of a substance. The standard battery includes tests aimed at detecting mutagenic, clastogenic and aneugenic effects. Any departures from established guidance shall be justified and the impact discussed.

II.6.3.6.3. Results of genotoxicity tests shall be used to evaluate whether a substance is likely to cause genetic damage that may be passed from a parent cell to its daughter cells, either by direct or indirect effects on deoxyribonucleic acid ('DNA').

II.6.3.6.4. Exposure to certain genotoxic substances is known to be associated with carcinogenesis and consequently, clearly positive findings in genotoxicity tests shall be considered to indicate that the substance may be carcinogenic. In addition, because germ cell mutations are known to be associated with disease, clearly positive findings in genotoxicity tests shall be considered to indicate that the substance may induce heritable disease (reproductive toxicity).

II.6.3.6.5. The deliberate use of genotoxic substances that interact directly with DNA shall not be accepted in medicines for food-producing animals.

II.6.3.6.6. The results from the genotoxicity tests shall contribute to the evaluation of the need for carcinogenicity data. Other factors that shall be considered in determining the need for carcinogenicity data shall be the existence of relevant structural alerts and the occurrence of pre-neoplastic findings in repeat dose toxicity tests.

II.6.3.6.7. A substance that directly induces clearly positive findings in genotoxicity tests may only be accepted for use in food-producing animals if the genotoxicity findings are demonstrated not to be of relevance for the consumer. Results from carcinogenicity studies demonstrating the absence of neoplasia may form part of such a demonstration. Mechanistic data shall also be needed in order to demonstrate that the mechanism underlying the observed genotoxicity is not relevant for the consumer.

II.6.3.6.8. In the absence of data to demonstrate that observed genotoxicity is not relevant for the consumer, clearly positive findings shall lead to the conclusion that an ADI cannot be established and that the substance is not appropriate for use in food-producing species.

II.6.3.6.9. Clearly negative results from a standard battery of genotoxicity tests shall lead to the conclusion that the substance is not genotoxic.

II.6.3.6.10. If equivocal results are seen in genotoxicity tests, the need for further testing shall be considered in light of the overall weight of evidence of the available data.

([1]) VICH GL32 Studies to evaluate the safety of residues of veterinary drugs in human food: developmental toxicity testing (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001479.jsp&mid=WC0b01ac058002dd37).

([2]) VICH GL23 Studies to evaluate the safety of residues of veterinary drugs in human food: genotoxicity testing (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001476.jsp&mid=WC0b01ac058002dd37).

II.6.3.6.11. In general the genotoxicity of major metabolites shall be considered to be adequately addressed by studies performed with the parent substance. However, if a major metabolite is produced in the target species but not in the laboratory animal species it may not be possible to conclude on the genotoxicity of residues without additional data generated using the relevant metabolite.

II.6.3.6.12. In principle, identification of minor metabolites shall not be required.

II.6.3.6.13. Minor metabolites are those present at levels below 100 μg/kg or that make up less than 10 % of the total residues as described in *VICH GL46: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues* ([1]).

II.6.3.6.14. If the structure of a minor metabolite is known or can be hypothesised and if the metabolite is or is expected to interact directly with DNA, then the potential risk for consumers shall be addressed. Evidence shall be provided to confirm that its level is low enough to be considered virtually safe — i.e. the level shall be low enough to ensure that the increased cancer risk that would result from consumer exposure to the substance would be less than 1 in 10^6. This shall be achieved either using chemical specific data or, in the absence of such data, using the threshold of toxicological concern ('TTC') concept which provides an approach for quantifying the risk associated with a given exposure to a substance. Guidance published by the EFSA and the WHO on the TTC approach shall be followed ([2]).

II.6.3.6.15. Similarly, if there is a concern that a minor metabolite present in food of animal origin is further metabolised in the consumer to produce a DNA reactive substance, evidence shall be provided to demonstrate that consumer exposure occurs at levels low enough to be considered virtually safe.

II.6.3.6.16. For any of these substances (potentially genotoxic minor metabolites produced in the target animal or in the human consumer), the level of residues present in food of animal origin shall result in consumer exposure below the TTC at all time points following the start of treatment. As the possibility of exposure before the withdrawal period cannot be ruled out, and in light of the serious non-threshold based effect, it shall not be enough to demonstrate depletion to levels compliant with the TTC by the time point at which residues fall below the proposed MRLs.

II.6.3.6.17. If more than one minor metabolite is DNA reactive, in the absence of evidence to the contrary it shall be assumed that all DNA reactive substances act by the same mode of action. Consequently, the total level of DNA reactive substances (dose addition) shall be compared with the TTC.

II.6.3.6.18. Substances and metabolites that may cause cancer by mechanisms other than direct interaction with DNA may be assumed to have threshold based mechanisms of action. If such substances are to be used in veterinary medicines for food-producing animals, NO(A)ELs or BMDLs shall be established for the relevant effects in appropriately justified studies.

II.6.3.7. Carcinogenicity

II.6.3.7.1. *Criteria for the selection of substances for carcinogenicity testing*

II.6.3.7.1.1. *VICH GL28: Studies to evaluate the safety of residues of veterinary drugs in human food: carcinogenicity testing* ([3]) provides guidance on factors to consider when determining the need for carcinogenicity testing and on carcinogenicity testing to be undertaken and this shall be followed. Any departures from established guidance shall be justified and the impact discussed.

([1]) VICH GL46 Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001516.jsp&mid=WC0b01ac058002dd37).

([2]) Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree (http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2016.EN-1006/epdf).

([3]) VICH GL28 Studies to evaluate the safety of veterinary drugs in human: carcinogenicity testing (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001477.jsp&mid=WC0b01ac058002dd37).

II.6.3.7.1.2. In those cases where carcinogenicity testing is deemed appropriate, the standard requirement shall be for a two-year rat study and an 18-month mouse study although, with appropriate justification, data from a single rodent species may be accepted.

II.6.3.7.1.3. Genotoxic carcinogens shall not be accepted for use in food-producing animals.

II.6.3.7.1.4. A substance that induces positive findings in carcinogenicity tests may only be accepted for use in food producing animals if the carcinogenicity data are demonstrated to be of no relevance for the consumer (for example, if the type of tumour seen is known to be of no relevance for humans) or if the carcinogenicity are demonstrated to be the result of a threshold dependent mechanism of action. In the latter case a NO(A)EL or BMDL for carcinogenicity shall be established.

II.6.3.7.1.5. If carcinogenicity testing is not undertaken, the absence of such data shall be scientifically justified and the impact of its absence discussed.

II.6.4. *Other requirements*

II.6.4.1. General principles

II.6.4.1.1. The need for safety data addressing other potential effects shall be determined on a case-by-case basis. VICH GL33 addresses the need for additional testing.

II.6.4.1.2. Factors to be taken into account when considering the need for such data include:

(a) the structure of the substance and its similarity to substances with known toxicological effects;

(b) the class of the substance and known toxicological properties of other substances in the class;

(c) the mode of action of the substance;

(d) any effects seen in the standard toxicity studies that warrant further investigation (e.g. immunotoxicity, neurotoxicity or endocrine dysfunction);

(e) the existence of published literature highlighting relevant findings, including literature relating to effects seen in humans exposed to the substance.

II.6.4.2. Special studies (e.g. immunotoxicity, neurotoxicity)

II.6.4.2.1 *Immunotoxicity*

II.6.4.2.1.1. If relevant effects are seen in repeated dose or other toxicity studies (e.g. changes in lymphoid organ weights and/or histology and changes in cellularity of lymphoid tissues, bone marrow or peripheral leukocytes) additional functional testing may be required. The investigator shall justify the nature of any additional testing, taking account of the observations noted in other toxicity studies.

II.6.4.2.1.2. For certain classes of substance (such as beta lactam antibiotics) which are known to elicit hypersensitivity (allergic) reactions in sensitive individuals data shall be provided on exposure levels that have been associated with hypersensitivity responses.

II.6.4.2.1.3. Details shall be provided of all immunological studies performed with the substance as part of any aspect of the assessment (e.g. sensitisation assays performed for user safety or efficacy studies performed on immune-modulatory substances). Any reports of adverse effects in humans shall also be provided.

II.6.4.2.1.4. Data obtained from such studies shall be taken into account when determining the toxicological ADI or alternative limit.

II.6.4.2.2. *Neurotoxicity, developmental neurotoxicity and delayed neurotoxicity*

II.6.4.2.2.1. Neurotoxicity testing shall be required where repeated dose studies indicate that there may be a relevant concern.

II.6.4.2.2.2. Substances that have been shown in other toxicological assays to cause histological, biophysical or biochemical changes to the nervous system, or to cause neuro-behavioural changes, shall also be tested for neurotoxicity. Physicochemical properties, structure-activity information and recorded adverse effects in humans may give further indication on the need for neurotoxicity tests.

II.6.4.2.2.3. Neurotoxicity testing shall be performed using the oral route and shall follow the advice given in the Organisation for Economic Cooperation and Development ('OECD') Guidelines for the Testing of Chemicals — Test Guideline 424 ([1]) on the methodology to be used in neurotoxicity studies in rodents. This study may be performed as a stand-alone study or may be incorporated in other repeated dose toxicity studies.

II.6.4.2.2.4. Although OECD Test Guideline 424 does not specifically address effects on the activity of acetylcholinesterase, this end point shall be included in all repeated dose toxicity studies for specific substances known or suspected to have such activity (for example, organophosphates or carbamates). Testing for cholinesterase inhibition shall at least include measurements in brain and erythrocytes.

II.6.4.2.2.5. If a substance has been shown to cause neuropathology or neurotoxicity in adults, or cause other types of toxicity indicative of nervous system involvement at a developmental stage, developmental neurotoxicity testing may be considered necessary. In such a case, OECD Test Guideline 426 ([2]) which advises on the methodology to be used in developmental neurotoxicity studies shall be followed. The extended one generation reproductive toxicity study (OECD Test Guideline 443 ([3])) also provides for developmental neurotoxicity testing.

II.6.4.2.2.6. Organophosphates shall be tested for delayed neurotoxicity in a hen assay that incorporates measurement of neuropathy target esterase ('NTE') in brain tissue. Both single exposure (OECD Test Guideline 418 ([4])) and repeated exposure (OECD Test Guideline 419 ([5])) shall be considered. While single dose studies performed according to OECD Test Guideline 418 may only allow identification of a delayed neurotoxicity effect, repeated dose studies (OECD Test Guideline 419) may allow identification of a NO(A)EL or BMDL.

II.6.4.2.2.7. The neurotoxicity studies shall allow the establishment of NO(A)ELs or LO(A)ELs or BMDL which shall be taken into account when determining the toxicological ADI or alternative limit.

II.6.4.3. Microbiological properties of residues

II.6.4.3.1. *Potential effects on the human gut flora*

II.6.4.3.1.1. For substances with antimicrobial activity, antimicrobial effects on the human intestinal flora may occur at doses below those seen to induce toxicity in the toxicity tests. For such substances, a microbiological ADI shall be established in line with *VICH GL36: Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish a microbiological ADI* ([6]).

II.6.4.3.1.2. The data shall be used to derive a microbiological ADI.

II.6.4.3.1.3. The risks that result from residues shall be clearly distinguished from the potential risk to public health associated with the ingestion of food of animal origin which contains resistant bacteria selected under the pressure of an antimicrobial therapy.

([1]) OECD Test No 424: Neurotoxicity Study in Rodents (http://www.oecd-ilibrary.org/environment/test-no-424-neurotoxicity-study-in-rodents_9789264071025-en).

([2]) OECD Test No 426: Developmental Neurotoxicity Study (http://www.oecd-ilibrary.org/environment/test-no-426-developmental-neurotoxicity-study_9789264067394-en)

([3]) OECD Test No 443: Extended One-Generation Reproductive Toxicity Study (http://www.oecd-ilibrary.org/environment/test-no-443-extended-one-generation-reproductive-toxicity-study_9789264185371-en).

([4]) OECD Test No 418: Delayed Neurotoxicity of Organophosphorus Substances Following Acute Exposure (http://www.oecd-ilibrary.org/environment/test-no-418-delayed-neurotoxicity-of-organophosphorus-substances-following-acute-exposure_9789264070905-en).

([5]) OECD Test No 419: Delayed Neurotoxicity of Organophosphorus Substances: 28-day Repeated Dose Study (http://www.oecd-ilibrary.org/environment/test-no-419-delayed-neurotoxicity-of-organophosphorus-substances-28-day-repeated-dose-study_9789264070929-en).

([6]) VICH GL36 Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001531.jsp&mid=WC0b01ac058002dd37).

II.6.4.3.1.4. As described in the VICH GL36, the following two endpoints of concern shall be addressed in relation to the establishment of a microbiological ADI:

(a) disruption of the colonisation barrier — the first endpoint of concern shall address the question of whether ingestion of residues of antimicrobiologically active substances in food of animal origin poses a risk to human health resulting from the disruption of the colonisation barrier function of the normal intestinal flora;

(b) increase of the population of resistant bacteria — the second endpoint of concern shall address the question of whether ingestion of residues of antimicrobiologically active substances pose a risk to human health resulting from an increase in the population of resistant bacteria either due to acquisition of resistance by previously sensitive bacteria or to a relative increase in the proportion of less sensitive organisms.

II.6.4.3.1.5. Any departures from the established guidance shall be justified and the impact discussed.

II.6.4.3.1.6. If no testing for effects on the human intestinal flora is undertaken, the absence of such data shall be scientifically justified and the impact of its absence discussed.

II.6.4.4. Observations in humans

II.6.4.4.1. Any available data on health effects seen in humans following exposure to the substance shall be provided. Such data may relate to intentional exposure of humans (e.g. when the substance is used in human medicine) or unintentional exposure (e.g. reports of occupational exposure). Such data may focus on epidemiological, pharmacological, toxicological or clinical findings.

II.6.4.4.2. The data related to exposure of humans may provide valuable additional information on the overall toxicological profile of the substance, as well as provide information on the comparative sensitivity of humans and animals, even if they cannot be used for derivation of the ADI. In some cases such data may be useful in supporting arguments relating to the relevance (or lack of relevance) of certain findings in laboratory animals.

II.6.5. *Findings of other EU or international scientific bodies*

II.6.5.1. If relevant safety evaluations of the substance have been undertaken by other EU or international scientific bodies including EFSA, ECHA, JECFA and FAO/WHO Joint Meetings on Pesticide Residues ('JMPR') this shall be highlighted, along with the conclusions reached.

II.6.6. *Determination of an ADI or alternative limit*

II.6.6.1. Determination of an ADI

Generally the ADI shall be derived from the pharmacological, toxicological or microbiological data although, where appropriate data exist, it may be derived from human data.

II.6.6.1.1. *Derivation of the toxicological ADI*

II.6.6.1.1.1. The toxicological ADI shall be derived by dividing the selected toxicological NO(A)EL/BMDL by an uncertainty factor, in order to take account of possible inter-species variation (i.e. differences in sensitivity of humans and laboratory animals) and intra-species variation (i.e. differences in sensitivity within the human population). The uncertainty factor may be adjusted to take other uncertainties into consideration, as necessary (see below).

II.6.6.1.1.2. The formula used to determine the toxicological ADI shall be as follows:

ADI (mg/kg bw/day) = NOAEL or BMDL (mg/kg bw/day) divided by Uncertainty Factor

II.6.6.1.1.3. The choice of the NO(A)EL or BMDL and the uncertainty factor shall be justified.

II.6.6.1.1.4. Unless otherwise justified, the toxicological ADI shall be derived from the lowest NO(A)EL or BMDL observed in the most sensitive species in the toxicology studies. In certain circumstances a justification for using an alternative starting point may be possible (for example, if data exist demonstrating that the effect seen at LO(A)EL in the most sensitive species is not relevant for humans).

II.6.6.1.1.5. If using the benchmark dose ('BMD') approach, the BMDL shall be used as the point of departure for derivation of the ADI. In most cases the choice of the critical endpoint is not expected to change when using the BMDL versus the NO(A)EL approach, since the same biological considerations apply.

II.6.6.1.1.6. In selecting the default values for the magnitude of the response for which the BMDL is derived (i.e. the benchmark response ('BMR')), on choice of the recommended dose-response models as well as on reporting the results of a BMD analysis, guidance found in the EFSA Scientific Opinion on Use of the benchmark dose approach in risk assessment ([1]) shall be followed.

II.6.6.1.1.7. In relation to uncertainty factors, the default assumption is that human beings may be up to 10 times more sensitive than the test animal species and that the difference in sensitivity within the human population is a tenfold range. Therefore, assuming appropriate studies are available, an uncertainty factor of 100 shall usually be applied.

II.6.6.1.1.8. Where the results of animal studies indicate teratogenic effects at doses that do not cause maternal toxicity, an overall uncertainty factor of up to 1 000 shall be applied to the NO(A)EL or BMDL for teratogenicity. For non-genotoxic threshold carcinogens an uncertainty factor of up to 1 000 may be used, depending on the mechanism involved.

II.6.6.1.1.9. It may occur that the most sensitive endpoint is observed in a species and/or study where all dose groups produce significant effects compared to the control group. In such cases the BMDL approach shall be recommended to establish the point of departure ('POD') from which to derive an ADI. Alternatively, if the effect observed in the lowest dose is a sufficiently minor response, it may be possible to establish an ADI based on this LO(A)EL. In this case an additional uncertainty factor of 2 to 5 shall be used to take into account that the LO(A)EL reference point is an unknown distance above the 'true' threshold.

II.6.6.1.1.10. The choice of uncertainty factors for use in deriving the ADI shall not depend on whether a NO(A)EL or a BMDL is taken as the POD.

II.6.6.1.1.11. Where the ADI is to be set on the basis of human data, there is no uncertainty factor to be applied for extrapolation from animals to humans. Thus, when using good quality human data from which to derive an ADI, it is appropriate to apply an uncertainty factor of only 10, to account for variation in individual responses between human beings.

II.6.6.1.1.12. The refinement of the standard approach for selecting uncertainty factors may be acceptable where adequate justification is provided. For example, the use of (metabolic) pathway related uncertainty factors may be appropriate to refine the standard uncertainty factor used for inter-individual (intra-species) variability.

II.6.6.1.1.13. Further refinement of the intra-species and inter-species tenfold uncertainty factors may be possible on a case-by-case basis, when toxicokinetic and toxicodynamic data support such adjustment factors.

II.6.6.1.1.14. For the multiplication of uncertainty factors the use of probabilistic approaches may be appropriate.

II.6.6.1.1.15. The use of these and other approaches for the refinement of standard uncertainty factors shall be fully justified.

II.6.6.1.1.16. Having regard to the previous considerations, the uncertainty factor used shall usually have a value between 10 and 1 000. Other values may be considered with appropriate justification.

II.6.6.1.2. *Derivation of the pharmacological ADI*

II.6.6.1.2.1. Pharmacological ADIs shall not be derived for all pharmacologically active substances as relevant pharmacological endpoints may be included in the toxicology studies. In such cases separate toxicological and pharmacological ADIs may not be needed.

([1]) Guidance of the Scientific Committee on Use of the benchmark dose approach in risk assessment (http://www.efsa.europa.eu/en/efsajournal/pub/1150).

II.6.6.1.2.2. Guidance on the need for a pharmacological ADI as provided for in the Committee for Medicinal Products for Veterinary Use ('CVMP') guideline on the approach to establish a pharmacological ADI ([1]) shall be followed. Where no pharmacological ADI is derived, justification for its absence shall be provided.

II.6.6.1.2.3. Where a pharmacological ADI is needed, the approach for its derivation shall be analogous to that described above under Section II.6.6.1.1 in relation to derivation of the toxicological ADI. The only difference is that the starting point used for derivation of the pharmacological ADI shall be the lowest NOEL or BMDL observed in the most sensitive species in the pharmacology studies.

II.6.6.1.3. *Derivation of a microbiological ADI*

II.6.6.1.3.1. As described in Section II.6.4.3 microbiological ADIs shall be derived for substances with antimicrobial activity. The methodologies for establishing a microbiological ADI are detailed in VICH GL 36 and shall be followed.

II.6.6.1.4. *The overall ADI*

Separate pharmacological, toxicological and microbiological ADIs shall be derived, as appropriate and the overall ADI (i.e. the ADI used in the risk assessment and in the setting of MRLs) shall generally be the lowest of the pharmacological, toxicological and microbiological ADIs.

II.6.6.1.5. *Substances with non-threshold effects*

For substances that may induce non-threshold effects, such as genotoxic carcinogens, derivation of a NO(A)EL or BMDL is not possible due to the uncertainty in establishing a threshold for these effects. For such substances an ADI cannot be derived.

II.6.6.2. Alternatives to the ADI

For some substances it may not be possible nor meaningful to establish an ADI. In such situations, alternatives to ADI may be used.

II.6.6.2.1. *Substances for which recommended dietary intake levels have been established*

II.6.6.2.1.1. For most minerals and trace elements there is a natural baseline level in human body compartments resulting from their uptake from food and other environmental sources, and element specific homeostatic or accumulation processes. It is important to discriminate between essential trace elements for which there is both a minimum daily dietary requirement and an upper acceptable intake level and non-essential elements which are considered as undesired or even toxic for humans.

II.6.6.2.1.2. The ADI approach is not appropriate for use in the assessment of essential elements as effects may occur at very low exposure levels, which represent a deficiency in supply. For most minerals and trace elements recommended dietary intake levels have been established by relevant scientific bodies (e.g. EU/EFSA; WHO). Daily dietary exposure estimates for essential elements may be compared with appropriate reference values, such as the recommended daily intake ('RDI'), dietary reference values ('DRVs', previously: recommended daily allowances ('RDA')), tolerable daily intakes ('TDIs') or tolerable weekly intakes ('TWIs') and provisional tolerable weekly intakes ('PTWI'). These values may be used in the risk assessment, in a way analogous to the ADI. The combined exposure resulting from treatment related residues and exposure from dietary and natural sources shall not exceed the respective reference values.

II.6.6.2.1.3. This approach may be appropriate for minerals, elements, vitamins and other natural constituents of food for which relevant recommended dietary intake levels have been established.

([1]) Approach to establish a pharmacological acceptable daily intake (ADI) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001530.jsp&mid=).

II.6.6.2.2. *Substances to which consumers are exposed via food or other sources and for which recommended intake levels have not been established*

II.6.6.2.2.1. When consumer exposure to residues of the active substance in food of animal origin is negligible or very low compared to the level of exposure that already occurs as a result of the presence of the material in the environment or already present in commodities (most notably foods), then it may be possible to argue that the impact (in terms of consumer exposure to residues) of the proposed use in veterinary medicinal products is negligible and that the establishment of an ADI shall not be necessary. A worst case estimate of residue levels that may occur as a result of the proposed use of the substance shall be provided, along with an estimate of the resulting consumer exposure. This shall be compared with the level of exposure known to occur via other sources. This approach may be particularly relevant for herbal medicines and vegetable extracts, as well as for natural organic acids (e.g. oxalic acid).

II.6.6.2.2.2. The chemical make-up of herbal/vegetable based products (including extracts) is typically complex and may be quite different to the make-up of residues that will remain in food commodities derived from treated animals. Due to the complexity of the parent material, it may not be practical or even possible to identify the resulting residues. For such substances, an alternative to the standard ADI based approach may be appropriate.

II.6.6.2.2.3. When using this approach it is important to exclude any possibility of non-threshold effects such as genotoxicity.

II.6.6.2.3. *Endogenous pharmacologically active substances*

II.6.6.2.3.1. If the pharmacologically active substance is identical to an endogenously produced molecule, it may be possible to demonstrate that the level of consumer exposure that occurs as a result of residues in food of animal origin is insignificant compared to the level of human exposure to the endogenous substance.

II.6.6.2.3.2. Human exposure to such substances may be expected to come from both exogenous (treatment related residues plus natural levels in food of animal origin) and endogenous (human physiological) origin. The risk assessment of the residues is complicated by the difficulty in assessing the likely response of ingestion of low exogenous levels when humans are constantly exposed to relatively high and fluctuating levels of endogenously produced substance and fluctuating dietary levels. In addition, for many active substances (like hormones, corticosteroids) exogenous exposure may lead to regulation of the endogenous production that, in turn, may change the endogenous hormone levels and the overall response. This complicates the interpretation of conventional toxicology studies and the derivation of an ADI. In addition, findings in laboratory animals may be difficult to extrapolate to the situation in humans owing to complex specific differences in biochemical/pharmacodynamic regulatory mechanisms.

II.6.6.2.3.3. Consumer exposure to residues may be best estimated by comparing treatment related excess intake of residues from food to intake of the substance from untreated animals (with natural background levels). This may then also be compared with the endogenous daily human production of the substance. Possible species specific differences (analogues) shall be discussed.

II.6.6.2.3.4. This approach may be appropriate for hormones and other endogenously produced substances.

II.6.6.2.4. *Substances that lack bioavailability*

II.6.6.2.4.1. For substances that are not absorbed following oral ingestion, systemic exposure is negligible (or even non-existent). For such substances it is not possible to establish a conventional oral NO(A)EL or BMDL and ADI. The risk assessment for these types of substances shall normally rely on demonstration of the absence of oral bioavailability in suitable models or, where appropriate, through proof of degradation and/or inactivation under gastric conditions (likely to be demonstrated in *in vitro* models). In addition, for such substances, possible local effects on the gastrointestinal system (including microbiological effects on the colonisation barrier) shall be addressed.

III. RESIDUE FILE

III.1. In general a full residue data package shall be required. If data are not provided for standard endpoints this shall be thoroughly justified.

III.2. **Detailed and critical summary**

III.2.1. A detailed and critical summary of the residues file shall be required for all applications.

III.2.2. The detailed and critical summary shall:

(a) include a clear position on the adequacy of the data presented, in light of current scientific knowledge;

(b) have an introduction describing the actual or proposed pattern of use of the substance under review in animal husbandry and a summary of any other experience of its use;

(c) consider the extent to which the substance concerned has similarities to other known substances, which may be relevant for the evaluation;

(d) cover all standard data requirements, as set out in Implementing Regulation (EU) 2017/12 provide a critical evaluation of the available experimental studies and an interpretation of the results;

(e) provide scientific justification for the omission of any standard studies;

(f) provide a description and explanation of the key findings for each study. The following issues shall be discussed: the animal species used (species, strain, sex, age, weight, etc.), test conditions (husbandry, diet, etc.), time points and numbers of animals per time point, milk and egg production if applicable, sampling (sampling size, collection and storage), and analytical methods used;

(g) summarise and discuss relevant scientific literature, including reports of evaluations undertaken by other scientific bodies (such as EFSA or JECFA). If detailed references to published scientific literature are used, all the requirements set out under General principles point 5 (I.5) shall be met, as far as possible;

(h) include information on the quality of batches of test substances used in the residue studies. Any association between findings and the quality of the test substances and/or the medicinal products shall be indicated. When necessary, a critical evaluation of the impurities present in the active ingredient shall be presented and information shall be provided on their potential influence on pharmacokinetics, metabolism, residue kinetics and analytical methods for the determination of residues. The implications of any differences of the chirality, chemical form and impurity profile between the substance used in the residues studies and the form to be marketed shall be discussed;

(i) discuss the GLP status of the studies submitted;

(j) discuss possible deficiencies in the design and conduct of the studies and their documentation, making reference to published Agency and other guidance. Any deviations from applicable guidance shall be highlighted and the impact of the deviation discussed and scientifically justified;

(k) comment on the use of experimental animals in the studies and whether the studies were conducted in accordance with Directive 2010/63/EU;

(l) justify the omission of particular studies and discuss the requirements for additional studies;

(m) provide a section on risk management considerations, addressing the issues described in Annex II below, and explaining the derivation of the proposed MRLs.

III.2.3. Annexes to the detailed and critical summary shall include:

(a) list of references — a list of all references shall be provided in accordance with internationally accepted standards. The references themselves shall be included in the dossier;

(b) tabulated study reports — tabular summaries of study reports to the detailed and critical summary shall be provided. In addition, a complete set of study reports shall be included in the dossier.

III.3. **Metabolism and residue kinetics in the target species**

III.3.1. Metabolism and residues data shall be required to characterise residues present in relevant food commodities, to demonstrate the time course of their depletion to a safe level (usually based on the ADI) and so to allow derivation of MRLs.

III.3.2. The data shall be provided in the form of a total residues depletion study providing quantitative data on the parent drug and its major metabolites in relevant food commodities, and the change in the levels of these over time. Total residues studies usually use radiolabelled drug although data from non-radiolabelled studies may be provided where appropriate (for example if the substance is known not to be metabolised). A separate marker residue depletion study shall often also be provided, using unlabelled drug and monitoring the depletion of the marker residue in relevant food commodities over time. Total residues and marker residue data may be provided by means of a single radiolabelled study that also uses an appropriately validated non-radiolabelled method to monitor depletion of the marker residue.

III.3.3. The test material shall contain the substance of concern in a representative concentration. It shall be administered by the intended route of administration of the proposed product, at the highest intended dose and for the maximum intended duration of treatment or for the time required for steady state to be achieved in edible tissues. Studies shall be conducted in animals that are representative of the proposed target populations.

III.3.4. Guidance provided in *VICH GL46: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues* ([1]) shall be followed in order to monitor (quantify) the depletion of total residues and key metabolites over time. These studies shall normally be performed using radiolabelled drug.

III.3.5. Guidance provided in *VICH GL49: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: validation of analytical methods used in residue depletion studies* ([2]) shall be followed in order to demonstrate the analytical method standards and in order to obtain marker residue depletion data of an acceptable quality.

III.3.6. Specific guidance relating to residue studies to be undertaken for substances intended for use in honey bees provided in *VICH GL56: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods* ([3]) shall be followed.

III.3.7. The total residues study (usually performed with radiolabelled drug) shall provide information on:

(a) the depletion of residues over time from relevant food commodities of treated animals;

(b) the identity of the major components of the total residues in relevant food commodities;

(c) the quantitative relationships between the major residue components and the total residues.

These data shall be used to establish the marker residue and the ratio of marker to total residues for each relevant food commodity.

([1]) VICH GL46 Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001516.jsp&mid=WC0b01ac058002dd37).

([2]) VICH GL49 Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: validation of analytical methods used in residue depletion studies (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001513.jsp&mid=WC0b01ac058002dd37).

([3]) VICH GL56 Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/safety_residues_pharmaceuticals/general_content_001815.jsp&mid=WC0b01ac058002dd37).

III.3.8. A suitable marker residue shall be identified. The marker residue may be the parent drug, any of its metabolites or a combination of any of these. The marker residue shall have the following properties:

(a) it shall have a known relationship between it and the total residue concentration in the edible tissue/food commodity of interest;

(b) it is appropriate for use in testing for the presence of residues at the time point of interest;

(c) it shall have a practicable analytical method to measure it at the level of the MRL.

III.3.9. The ratio of marker to total residues describes the relationship between the marker residue and total residues in each relevant food commodity. This ratio may be different in different food commodities and, as it may vary over time, it shall be established until the time corresponding to that at which residues of concern are expected to be below the ADI. The ratio of marker to total residues shall be used in the intake calculation to calculate potential consumer exposure to total residues from data relating to the marker residue.

III.3.10. By monitoring the depletion of total residues in the edible tissues/food commodities, the time point at which total residues deplete to below the ADI (or the fraction of the ADI available for use) shall be established. In each tissue/food commodity, the concentration of the selected marker residue at this time point shall be taken as the starting point from which the MRL shall be developed.

III.3.11. Information from the metabolism study shall also allow comparison of the metabolites produced in the target animal species with those produced in the laboratory animals species in order to ensure that the major residues to which consumers will be exposed (i.e. the major metabolites produced in the target species) were adequately tested in the laboratory animal toxicity studies.

III.3.12. Any departures from established guidance shall be justified and the impact discussed.

III.4. **Monitoring and exposure data, if relevant**

III.4.1. Monitoring or exposure data of the pharmacologically active substance shall not be required. However, if available, it may provide valuable additional information in certain cases, i.e. for substances that are already present in the environment (either naturally or as a result of use in the veterinary or other sectors). Such data may be useful in determining background levels to which consumers may already be exposed. If such data are available, whether as published results from official residue monitoring bodies or as results of academic or other research, these shall be provided.

III.5. **Residue analytical method**

III.5.1. A validation report of the analytical method used for quantification of the marker residue in the residues study shall be provided. Validation shall demonstrate that the analytical method complies with the criteria applicable for the relevant performance characteristics. The specific guidance on validation of analytical methods is provided in VICH GL49 shall be followed.

III.5.2. Analytical methods shall be provided at least for those food commodities and species in which MRLs are requested.

III.5.3. The availability of standards shall be confirmed and contact details provided in order to allow an exchange of information, if necessary, between representatives of the EU and national reference laboratory staff and the company.

III.5.4. Any departures from the requirements above shall be justified and the impact discussed.

III.5.5. The analytical method shall be evaluated for compliance with VICH GL49 and the additional points raised above. In addition, the Agency shall consult the European Reference Laboratory for control of residues for the particular substance type on the adequacy of the available methods and validation data.

III.5.6. Following the Agency's opinion, the validation data may be shared with other EU and national reference laboratories in order to facilitate development of appropriate methods by those authorities.

III.6. **Potential effects on the microorganisms used for industrial food processing**

III.6.1. The residues evaluation shall include an assessment of the potential effects of microbiologically active residues on microorganisms used for industrial food processing, in particular as regards the manufacture of dairy products.

III.6.2. The data shall be used to establish a residue concentration without effect on starter cultures. This shall be taken into consideration when deriving MRLs, to ensure that residues present in relevant food commodities (i.e. milk) are not present at levels that impact on dairy starter cultures.

III.6.3. The studies to be performed shall follow Agency's guidance for the assessment of the effect of antimicrobial substances on dairy starter cultures ([1]).

III.6.4. Any departures from the established guidance shall be justified and the impact discussed.

III.6.5. If no testing of microorganisms used for industrial food processing is undertaken, the absence of such data shall be scientifically justified and the impact of its absence discussed.

III.7. **Findings of other EU or international scientific bodies**

III.7.1. If relevant residues evaluations of the substance have been undertaken by other EU or international scientific bodies including EFSA, ECHA, JECFA and JMPR this shall be presented, along with the conclusions reached.

([1]) Note for guidance for the assessment of the effect of antimicrobial substances on diary starter cultures (http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500004533&mid=WC0b01ac058009a3dc).

ANNEX II

Methodological principles for the risk management recommendations referred to in Article 7 of Regulation (EC) No 470/2009

I. ELABORATION OF MRLs

I.1. Derivation of numerical MRLs

I.1.1. Where it is considered appropriate in accordance with this Regulation to establish numerical MRL values, MRLs shall routinely be recommended for the edible tissues listed below:

(a) for mammals other than swine: muscle, fat, liver and kidney;

(b) for swine and poultry: muscle, fat and skin in natural proportions, liver and kidney;

(c) for fin-fish: muscle and skin in natural proportions;

(d) if the substance is proposed for use in a milk producing, egg producing or honey producing species, MRLs shall be recommended for milk, eggs and/or honey, respectively, wherever possible. As for tissues, recommendations for MRLs in milk, eggs and honey shall be based on data demonstrating the residue depletion profile in these commodities. Where no such data are available, it may be considered necessary to reserve an unused portion of the ADI for the future establishment of MRLs in these commodities (Section II.5).

I.1.2. When determining the MRLs, consideration shall be given to the following issues:

(a) the ADI (or alternative limit if appropriate) — MRLs shall be recommended at levels that ensure that consumer exposure to residues of concern remains below the ADI;

(b) the proposed marker residue;

(c) the ratio of the marker residue to total residues;

(d) the distribution of residues across edible tissues — the individual MRLs proposed for the different edible tissues shall reflect the distribution of residues across these tissues. In those cases where residues in a tissue rapidly fall below the limit of quantification (the smallest measured content of an analyte above which a determination of the analyte can be made with a specified degree of accuracy and precision) of the analytical method, it shall not be possible to establish MRLs that reflect the distribution of residues across tissues. Where this occurs, MRLs shall be set at twice the limit of quantification in order to provide an MRL for use in residue surveillance. Wherever possible, the tissue selected for residue monitoring purposes shall be one in which the MRL was set taking the distribution of residues across tissues into account;

(e) the overall exposure of the consumer to residues — this shall be demonstrated to be below the ADI based on the residue levels seen in the depletion studies, and using the standard food basket (see below).

I.1.3. In deriving MRLs it shall be assumed that the consumer will eat a standard food basket of animal-derived products every day. Consumer safety shall be ensured by keeping the total amount of residues in the standard food basket below the ADI.

The standard food basket shall be made up of the quantities of the food commodities shown in the table below:

Mammals		Poultry		Fish		Bees	
Muscle	0,300 kg	Muscle	0,300 kg	Muscle and skin in natural proportions	0,300 kg	Honey	0,020 kg
Fat	0,050 kg [1]	Fat and skin in natural proportions	0,090 kg				

Mammals		Poultry		Fish		Bees	
Liver	0,100 kg	Liver	0,100 kg				
Kidney	0,050 kg	Kidney	0,010 kg				
Milk	1,500 kg	Eggs	0,100 kg				

([1]) Fat and skin in natural proportions for pigs

I.1.4. Using the residue depletion data, the total residue burden in the standard food basket shall be calculated based on the observed residue levels at each time point on the residue depletion curve, so that the time point at which the total residue burden falls below the ADI is established. If the full ADI is available then these residue levels, rounded up as appropriate (usually to the nearest 50 μg/kg for tissues), shall be considered as potential MRLs. Consideration shall also be given to the factors listed under Section II points 1 to 7 and, if appropriate (e.g. if less than the full ADI is available), a subsequent time point on the residue depletion curve shall be used as the point from which to derive the MRLs.

I.1.5. Once MRL levels have been derived, the Theoretical Maximum Daily Intake ('TMDI') of residues shall be calculated using the standard food basket and assuming that residues are present in all food commodities at the level of the proposed MRLs. The TMDI is calculated by adding exposure to residues from all tissues obtained using the following calculation:

Amount per edible tissue or product = (proposed MRL for the tissue or product x (times) daily consumption of the tissue or product)/(divided by) Ratio of the marker to total residue in the tissue or product.

I.2. **The 'No MRL required' classification**

I.2.1. A 'No MRL required' classification may be recommended in those cases where it is clear that the establishment of numerical MRLs is not necessary for the protection of the consumer. The consumer exposure to residues shall always remain at safe levels (below the ADI or alternative limit) in order for a 'No MRL required' classification to be recommended.

I.2.2. Substances may be regarded as candidates for a 'No MRL required' status, if they fulfil one or more of the criteria stated below. It shall be noted, however, that fulfilment of one or more of these criteria shall not be regarded as automatically implying that a 'No MRL required' status shall be recommended. The following specificities of each individual substance shall be fully evaluated before reaching a conclusion:

(a) substances of endogenous origin, particularly if exposure to residues has only a minor impact on the overall exposure to the substance;

(b) substances which are essential nutrients or normal constituents of the diet in man and animals;

(c) substances for which no pharmacological activity considered to be biologically relevant has been identified;

(d) substances that have been demonstrated to be of low toxicity following exposure by the oral route;

(e) substances that are not absorbed or are poorly absorbed from the gastro-intestinal tract or from the sites of local application (e.g. skin or eyes);

(f) substances that are rapidly and extensively detoxified or excreted;

(g) substances that have been demonstrated not to result in detectable residues in food derived from treated animals.

I.2.3. In some cases a 'No MRL required' recommendation may incorporate a restriction on the way the substance is to be used (for example, a restriction 'for cutaneous use only' may be recommended in cases where it is clear that no residues of concern will result following cutaneous use, but the possibility of harmful residues cannot be ruled out following administration of the substance by a different route).

II. AVAILABILITY OF ALTERNATIVE MEDICINES AND OTHER LEGITIMATE FACTORS

II.1. **Availability of alternative medicines**

The need for the substance in order to avoid unnecessary suffering for target animals or to ensure the safety of those treating them may be relevant factors to consider in those cases where practical treatment alternatives are lacking. These considerations may justify acceptance of a reduced data package in line with the recommendations provided in the Agency's '*Guideline on safety and residue data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market*' ([1]). These factors may also be considered in relation to the need to set MRLs at levels that will allow development of a product with a practicable withdrawal period, as defined in Directive 2001/82/EC of the European Parliament and of the Council ([2]).

II.2. **Technological aspects of food and feed productions**

II.2.1. Where relevant, consideration shall be given to the possibility that microbiologically active residues impact on microorganisms used for industrial food processing, in particular as regards the manufacture of dairy products.

II.2.2. Information on testing that shall be considered in order to address this issue is detailed in Annex I Section III.6.

II.2.3. The recommended MRLs shall be set at levels that ensure that food processing is not adversely affected (e.g. dairy starter cultures).

II.3. **Feasibility of controls**

II.3.1. For some substances, for which setting numerical MRLs is not practicable (e.g. substances that may be naturally present in animal produce), the feasibility of undertaking residue control shall be considered on a case-by-case basis. This shall be determined based on the consideration of the potential risk posed to the consumer.

II.3.2. In cases where the time taken for residues to deplete to the recommended MRL may be longer in one (or more) tissue type than in others, it shall be recommended that, if the entire carcass is available, the tissues selected for monitoring of residues shall be those in which depletion of residues to the level of the MRL is slowest, as compliance with the MRL in this tissue will indicate compliance with the MRLs in other tissues also. This is particularly likely in those cases where residues are seen to be low in one or more tissues at all-time points and consequently the recommended MRL values for this (or these) tissue(s) are based on the limit of quantification of the analytical method.

II.4. **Conditions of use and application of the substances in veterinary medicinal products, good practice in the use of veterinary medicinal products and biocidal products, the likelihood of misuse or illegal use and other relevant factors**

II.4.1. For substances proposed for use in species that produce milk or eggs, consideration shall be given to the possibility of recommending MRLs in these commodities. Where MRLs cannot be recommended in milk or eggs for safety reasons, it shall be stated that use of the substance shall be restricted to animals not producing milk or eggs for human consumption.

II.4.2. If appropriate, consideration shall be given to recommending a restriction on the use of the substance. For example, if the residue data provided relate only to cutaneous application of the substance and there are concerns that residue levels in food of animal origin would be considerably higher if the substance were applied by another route, then consideration shall be given to recommending that use of the substance be restricted to cutaneous use.

II.4.3. If establishment of MRLs may increase the likelihood of misuse or illegal use of the substance (for example in relation to use as a growth promoter) this shall be clearly stated. Similarly, if the establishment of MRLs may increase good practice and limit misuse or illegal use this may also be stated.

([1]) Safety and residue data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001536.jsp&mid=WC0b01ac058002dd38).

([2]) Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).

II.4.4. Other factors may be considered on a case-by-case basis where evidence exists to indicate that there is a specific relevant concern regarding the use of the pharmacologically active substance. As a general principle, MRL assessments do not consider the effects of food processing (particularly cooking) on residues. However, if data are available indicating that food processing can be expected to increase levels of residues of concern, consideration shall be given to the potential impact on consumer health.

II.5. **Need for an unused portion of the ADI**

II.5.1. Since it is not possible to predict, with certainty, the future use of a substance in other species and with a view to increasing availability of veterinary medicinal products, as a general principle, it shall be considered that, unless MRLs are proposed in all food commodities included in the standard food basket, an adequate portion of the ADI shall remain unused.

II.5.2. MRL applications usually focus on tissues, however, potential future uses in milk, eggs and honey shall be considered. In general, a part of the ADI shall be reserved for future uses and MRLs that use the full ADI shall only be accepted in exceptional cases.

II.5.3. When considering the need to maintain an unused portion of the ADI, a number of substance specific factors shall be considered, including:

(a) information relating to the likely usefulness of the substance in other species (e.g. indication in the original species, mechanism of action, known toxicity of the substance in different species);

(b) physico-chemical and pharmacokinetic data that may indicate the likely distribution of the substance to milk, eggs or honey;

(c) whether the intended use of the substance requires MRLs that use up almost the entire ADI and are there particular considerations (such as availability concerns) that would justify recommending MRLs that would limit the possibility for future development of the substance;

(d) consideration of existing uses of the substance in fields other than veterinary medicine, and the consumer exposure that may result from these uses (indicated under Section II.6).

II.6. **Exposure from other sources (combined exposure to dual-use substances)**

II.6.1. In order to ensure that all sources of consumer exposure to the substance are considered, all known uses of the substance shall be considered and the consumer exposure that results from these uses shall be estimated. MRLs shall be proposed at levels that ensure that the total amount of residues from all sources likely to be ingested do not exceed the ADI.

II.6.2. In the case of substances also used as plant protection products, a general guidance figure for the portion of the ADI that may be reserved for veterinary use shall be 45 % of the ADI.

II.6.3. Where the existing pesticide product authorisation allows and sufficient data are available on intake from plant protection use, it may be possible to allocate a larger part to veterinary use without exceeding the ADI. In order to identify the proportion of the ADI that is available, the MRL approved for the plant protection product shall be taken into account.

II.6.4. As the methodology used in establishing MRLs for edible tissues for plant protection products differs to that used for veterinary use, care shall be taken when combining the estimated exposure risk from the different methodologies.

II.6.5. For dual-use substances used as biocides in animal husbandry, the CVMP Guideline on risk characterisation and assessment of maximum residue limits (MRL) for biocides ([1]) shall be followed.

II.6.6. With regard to feed additives, consultation with the European Union Register of Feed Additives shall indicate if the substance has been authorised for use in animal feed. When evaluating such substances, EFSA shall be consulted.

([1]) Risk characterisation and assessment of maximum residue limits (MRL) for biocides (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001541.jsp&mid=WC0b01ac05804aca04).

II.7. **Injection site residues**

II.7.1. The muscle MRL shall be set at a level for monitoring of residues in non-injection site muscle, as consumers routinely ingest non-injection site muscle and rarely ingest injection site muscle.

II.7.2. For those injectable substances for which depletion of injection site residues when compared to the muscle MRL would result in extended (prohibitive) withdrawal periods, an Injection Site Residue Reference Value ('ISRRV') shall also be established by the Agency. The ISRRV shall be set at a level that ensures that, at the likely withdrawal period, a standard food basket including 300g of injection site muscle would contain residues below the ADI.

II.7.3. The ISRRV shall not be published in the Annex to Regulation (EU) No 37/2010; the value shall only be available in the European Public MRL Assessment Report ('EPMAR') and shall be used when deriving a withdrawal period for the veterinary medicinal product.

III. CONSIDERATIONS ON POSSIBLE EXTRAPOLATION OF MRLs

III.1. The extrapolation of MRLs shall be considered in line with the requirements as set out in the Commission Regulation (EU) 2017/880 ([1]).

III.2. Data that may be useful in relation to the extrapolation considerations shall be submitted as part of the dossier, where available.

([1]) Commission Regulation (EU) 2017/880 of 23 May 2017 laying down rules on the use of a maximum residue limit established for a pharmacologically active substance in a particular foodstuff for another foodstuff derived from the same species and a maximum residue limit established for a pharmacologically active substance in one or more species for other species, in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council (OJ L 135, 24.5.2017, p. 1).

COMMISSION IMPLEMENTING REGULATION (EU) 2018/783

of 29 May 2018

amending Implementing Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance imidacloprid

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC ([1]), and in particular Article 21(3), Article 49(2) and Article 78(2) thereof,

Whereas:

(1) The active substance imidacloprid was included in Annex I to Council Directive 91/414/EEC ([2]) by Commission Directive 2008/116/EC ([3]).

(2) Active substances included in Annex I to Directive 91/414/EEC are deemed to have been approved under Regulation (EC) No 1107/2009 and are listed in Part A of the Annex to Commission Implementing Regulation (EU) No 540/2011 ([4]).

(3) Commission Implementing Regulation (EU) No 485/2013 ([5]) amended the conditions of approval of the active substance imidacloprid and required the applicant to provide confirmatory information as regards:

(a) the risk to pollinators other than honey bees;

(b) the risk to honey bees foraging in nectar or pollen in succeeding crops;

(c) the potential uptake via roots to flowering weeds;

(d) the risk to honey bees foraging on insect honey dew;

(e) the potential guttation exposure and the acute and the long-term risk to colony survival and development, and the risk to bee brood resulting from such exposure;

(f) the potential exposure to dust drift following drill and the acute and the long-term risk to colony survival and development, and the risk to bee brood resulting from such exposure;

(g) the acute and long-term risk to colony survival and development and the risk to bee brood for honeybees from ingestion of contaminated nectar and pollen.

(4) In December 2014, the applicant submitted additional information concerning bees (i.e. honey bees, bumble bees and solitary bees) to the rapporteur Member State Germany within the time period provided for its submission.

(5) Germany assessed the additional information submitted by the applicant. It submitted its assessment, in the form of an addendum to the draft assessment report, to the other Member States, the Commission and the European Food Safety Authority ('the Authority') on 18 January 2016.

(6) The Commission consulted the Authority which presented its conclusion on the risk assessment of imidacloprid on 13 October 2016 ([6]). The Authority identified for most crops high acute risks for bees from plant protection

([1]) OJ L 309, 24.11.2009, p. 1.
([2]) Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market (OJ L 230, 19.8.1991, p. 1).
([3]) Commission Directive 2008/116/EC of 15 December 2008 amending Council Directive 91/414/EEC to include aclonifen, imidacloprid and metazachlor as active substances (OJ L 337, 16.12.2008, p. 86).
([4]) Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances (OJ L 153, 11.6.2011, p. 1).
([5]) Commission Implementing Regulation (EU) No 485/2013 of 24 May 2013 amending Implementing Regulation (EU) No 540/2011, as regards the conditions of approval of the active substances clothianidin, thiamethoxam and imidacloprid, and prohibiting the use and sale of seeds treated with plant protection products containing those active substances (OJ L 139, 25.5.2013, p. 12).
([6]) EFSA (European Food Safety Authority), 2016. Peer review of the pesticide risk assessment for the active substance imidacloprid in light of confirmatory data submitted. *EFSA Journal* 2016;14(11):4607. doi: 10.2903/j.efsa.2016.4607.

products containing the active substance imidacloprid. In particular, as regards exposure via dust, the Authority identified high risks for bees for several field uses. For bees foraging in the treated crop, a high risk was identified for the use on potatoes and winter cereals. For almost all field uses, a high risk to bees was also identified in the succeeding crops. In addition, the Authority identified a number of data gaps.

(7) As foreseen in recital 16 of Implementing Regulation (EU) No 485/2013, the Commission initiated a review of new scientific information on 11 February 2015 by mandating EFSA to organise an open call for data. EFSA launched an open call for data which ended on 30 September 2015 ([1]).

(8) On 13 November 2015, the Commission requested EFSA to provide conclusions concerning an updated risk assessment for bees as regards the use of imidacloprid applied as a seed treatment or granules by organising a peer review and taking into account the data collected in the framework of the specific open call for data and any other new data from studies, research and monitoring activities that are relevant to the uses under consideration. The Authority presented its conclusion on the peer review of the updated pesticide risk assessment for bees for the active substance imidacloprid considering the uses as seed treatment and granules on 28 February 2018 ([2]). The applicant was given the opportunity to comment on this conclusion. The applicant submitted its comments which have been carefully examined.

(9) The draft assessment report, the addendum to the draft assessment report and the conclusions of the Authority were reviewed by the Member States and the Commission within the Standing Committee on Plants, Animals, Food and Feed and finalised on 27 April 2018 in the form of a revised addendum to the Commission review report for imidacloprid.

(10) The Commission invited the applicant to submit its comments on the revised addendum to the review report for imidacloprid. The applicant submitted its comments which have been carefully examined.

(11) Having reviewed the information submitted by the applicant in 2014 the Commission has concluded that the further confirmatory information required by Implementing Regulation (EU) No 485/2013 has not been provided, and having also considered the conclusion on the updated risk assessment for bees, the Commission has concluded that further risks to bees cannot be excluded without imposing further restrictions. Bearing in mind the need to ensure a level of safety and protection consistent with the high level of protection of animal health that is sought within the Union, it is appropriate to prohibit all outdoor uses. Therefore, it is appropriate to limit the use of imidacloprid to permanent greenhouses and to require that the resulting crop stays its entire life cycle within a permanent greenhouse, so that it is not replanted outside.

(12) The Annex to Implementing Regulation (EU) No 540/2011 should therefore be amended accordingly.

(13) Taking into account the risks for bees from treated seeds, the placing on the market and the use of seeds treated with plant protection products containing imidacloprid should be subject to the same restrictions as the use of imidacloprid. It is therefore appropriate to provide that seeds treated with plant protection products containing imidacloprid shall not be placed on the market or used, except where the seeds are intended to be used only in permanent greenhouses and the resulting crop stays in a permanent greenhouse during its entire life cycle.

(14) Member States should be allowed sufficient time to amend or withdraw authorisations for plant protection products containing imidacloprid.

(15) For plant protection products containing imidacloprid, where Member States grant a grace period pursuant to Article 46 of Regulation (EC) No 1107/2009, that period should, at the latest, expire on 19 December 2018.

(16) The prohibition of placing on the market and use of treated seeds should apply only as of 19 December 2018 in order to allow for a sufficient period of transition.

(17) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Plants, Animals, Food and Feed,

([1]) EFSA (European Food Safety Authority), 2015. Technical report on the open call for new scientific information as regards the risk to bees from the use of the three neonicotinoid pesticide active substances clothianidin, imidacloprid and thiamethoxam applied as seed treatments and granules in the EU. EFSA supporting publication 2015:EN-903. 8pp.

([2]) EFSA (European Food Safety Authority), 2018. Conclusions on the peer review of the pesticide risk assessment for bees for the active substance imidacloprid considering the uses as seed treatments and granules. *EFSA Journal* 2018;16(2):5178. 113 pp.

HAS ADOPTED THIS REGULATION:

Article 1

Amendment to Implementing Regulation (EU) No 540/2011

Part A of the Annex to Implementing Regulation (EU) No 540/2011 is amended in accordance with the Annex to this Regulation.

Article 2

Prohibition of the placing on the market and use of treated seeds

Seeds treated with plant protection products containing imidacloprid shall not be placed on the market or used, except where:

(a) the seeds are intended to be used only in permanent greenhouses; and

(b) the resulting crop stays within a permanent greenhouse during its entire life cycle.

Article 3

Transitional measures

Member States shall, in accordance with Regulation (EC) No 1107/2009, where necessary amend or withdraw existing authorisations for plant protection products containing imidacloprid as active substance by 19 September 2018 at the latest.

Article 4

Grace period

Any grace period granted by Member States in accordance with Article 46 of Regulation (EC) No 1107/2009 shall be as short as possible and shall expire by 19 December 2018 at the latest.

Article 5

Amendment to Implementing Regulation (EU) No 485/2013

As regards seeds which have been treated with plant protection products containing imidacloprid, Article 2 of Implementing Regulation (EU) No 485/2013 is deleted.

Article 6

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

However, Article 2 and Article 5 shall apply as of 19 December 2018.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 29 May 2018.

For the Commission

The President

Jean-Claude JUNCKER

ANNEX

The column 'Specific provisions' of row 216, imidacloprid, of Part A of the Annex to Implementing Regulation (EU) No 540/2011 is replaced by the following:

'PART A

Only uses as insecticide, in permanent greenhouses or for the treatment of seeds intended to be used only in permanent greenhouses, may be authorised. The resulting crop must stay within a permanent greenhouse during its entire life cycle.

PART B

For the implementation of the uniform principles as referred to in Article 29(6) of Regulation (EC) No 1107/2009, the conclusions of the review report on imidacloprid, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 26 September 2008 and the conclusions of the revised addendum of the review report on imidacloprid as finalised in the Standing Committee on Plants, Animals, Food and Feed on 27 April 2018 shall be taken into account.

In this overall assessment Member States must pay particular attention to:

— the risk to bees and bumble bees released for pollination in permanent greenhouses,

— the impact on aquatic organisms,

— the exposure of bees via the consumption of contaminated water from the permanent greenhouses.

Member States shall ensure that the seed coating shall only be performed in professional seed treatment facilities. Those facilities must apply the best available techniques in order to ensure that the release of dust during application to the seed, storage, and transport can be minimised.

Conditions of use shall include risk mitigation measures, where appropriate.'

COMMISSION IMPLEMENTING REGULATION (EU) 2018/784

of 29 May 2018

amending Implementing Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance clothianidin

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC ([1]), and in particular Article 21(3), Article 49(2) and Article 78(2) thereof,

Whereas:

(1) The active substance clothianidin was included in Annex I to Council Directive 91/414/EEC ([2]) by Commission Directive 2006/41/EC ([3]).

(2) Active substances included in Annex I to Directive 91/414/EEC are deemed to have been approved under Regulation (EC) No 1107/2009 and are listed in Part A of the Annex to Commission Implementing Regulation (EU) No 540/2011 ([4]).

(3) Commission Implementing Regulation (EU) No 485/2013 ([5]) amended the conditions of approval of the active substance clothianidin and required the applicants to provide confirmatory information as regards:

(a) the risk to pollinators other than honey bees;

(b) the risk to honey bees foraging in nectar or pollen in succeeding crops;

(c) the potential uptake via roots to flowering weeds;

(d) the risk to honey bees foraging on insect honey dew;

(e) the potential guttation exposure and the acute and the long-term risk to colony survival and development, and the risk to bee brood resulting from such exposure;

(f) the potential exposure to dust drift following drill and the acute and the long-term risk to colony survival and development, and the risk to bee brood resulting from such exposure;

(g) the acute and long term risk to colony survival and development and the risk to bee brood for honeybees from ingestion of contaminated nectar and pollen.

(4) In December 2014, the applicants submitted additional information concerning bees (i.e. honey bees, bumble bees and solitary bees) to the rapporteur Member State Belgium within the time period provided for its submission. They provided updated dossiers in March 2015 and June 2015.

(5) Belgium assessed the additional information submitted by the applicants. It submitted its assessment, in the form of an addendum to the draft assessment report, to the other Member States, the Commission and the European Food Safety Authority ('the Authority') on 31 August 2015.

([1]) OJ L 309, 24.11.2009, p. 1.
([2]) Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market (OJ L 230, 19.8.1991, p. 1).
([3]) Commission Directive 2006/41/EC of 7 July 2006 amending Council Directive 91/414/EEC to include clothianidin and pethoxamid as active substances (OJ L 187, 8.7.2006, p. 24).
([4]) Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances (OJ L 153, 11.6.2011, p. 1).
([5]) Commission Implementing Regulation (EU) No 485/2013 of 24 May 2013 amending Implementing Regulation (EU) No 540/2011, as regards the conditions of approval of the active substances clothianidin, thiamethoxam and imidacloprid, and prohibiting the use and sale of seeds treated with plant protection products containing those active substances (OJ L 139, 25.5.2013, p. 12).

(6) The Commission consulted the Authority which presented its conclusion on the risk assessment of clothianidin on 13 October 2016 ([1]). The Authority identified for most crops high acute risks for bees from plant protection products containing the active substance clothianidin. In particular, as regards exposure via dust, the Authority identified high acute risks for bees for winter cereals and high chronic risks to bees cannot be excluded for sugar beets. For the consumption of residues in contaminated pollen and nectar, high acute and chronic risks were identified or a high risk cannot be excluded for most field uses. Chronic and acute risks to bees were also identified in the succeeding crops for all field uses. For forestry nursery, no data was provided by the applicants and risks to bees can therefore not be excluded. Furthermore the Authority identified a number of data gaps.

(7) As foreseen in recital (16) of Implementing Regulation (EU) No 485/2013, the Commission initiated a review of new scientific information on 11 February 2015 by mandating EFSA to organise an open call for data. EFSA launched an open call for data which ended on 30 September 2015 ([2]).

(8) On 13 November 2015, the Commission requested EFSA to provide conclusions concerning an updated risk assessment for bees as regards the use of clothianidin applied as a seed treatment or granules by organising a peer review and taking into account the data collected in the framework of the specific open call for data and any other new data from studies, research and monitoring activities that are relevant to the uses under consideration. The Authority presented its conclusion on the peer review of the updated pesticide risk assessment for bees for the active substance clothianidin considering the uses as seed treatment and granules on 28 February 2018 ([3]). The applicants were given the opportunity to comment on this conclusion. The applicants submitted their comments which have been carefully examined.

(9) The draft assessment report, the addendum to the draft assessment report and the conclusions of the Authority were reviewed by the Member States and the Commission within the Standing Committee on Plants, Animals, Food and Feed and finalised on 27 April 2018 in the form of a revised addendum to the Commission review report for clothianidin.

(10) The Commission invited the applicants to submit their comments on the revised addendum to the review report for clothianidin. The applicants submitted their comments which have been carefully examined.

(11) Having reviewed the information submitted by the applicants in 2014 and 2015 the Commission has concluded that the further confirmatory information required by Implementing Regulation (EU) No 485/2013 has not been provided, and having also considered the conclusion on the updated risk assessment for bees, the Commission has concluded that further risks to bees cannot be excluded without imposing further restrictions. Bearing in mind the need to ensure a level of safety and protection consistent with the high level of protection of animal health that is sought within the Union, it is appropriate to prohibit all outdoor uses. Therefore, it is appropriate to limit the use of clothianidin to permanent greenhouses and to require that the resulting crop stays its entire life cycle within a permanent greenhouse, so that it is not replanted outside.

(12) The Annex to Implementing Regulation (EU) No 540/2011 should therefore be amended accordingly.

(13) Taking into account the risks for bees from treated seeds, the placing on the market and the use of seeds treated with plant protection products containing clothianidin should be subject to the same restrictions as the use of clothianidin. It is therefore appropriate to provide that seeds treated with plant protection products containing clothianidin shall not be placed on the market or used, except where the seeds are intended to be used only in permanent greenhouses and the resulting crop stays within a permanent greenhouse during its entire life cycle.

([1]) EFSA (European Food Safety Authority), 2016. Conclusion on the peer review of the pesticide risk assessment for the active substance clothianidin in light of confirmatory data submitted. *EFSA Journal* 2016;14(11):4606, 34 pp. doi:10.2903/j.efsa.2016.4606.

([2]) EFSA (European Food Safety Authority), 2015. Technical report on the open call for new scientific information as regards the risk to bees from the use of the three neonicotinoid pesticide active substances clothianidin, imidacloprid and thiamethoxam applied as seed treatments and granules in the EU. EFSA supporting publication 2015:EN-903. 8pp.

([3]) EFSA (European Food Safety Authority), 2018. Conclusions on the peer review of the pesticide risk assessment for bees for the active substance clothianidin considering the uses as seed treatments and granules. *EFSA Journal* 2018;16(2):5177. 86 pp.

(14) Member States should be allowed sufficient time to amend or withdraw authorisations for plant protection products containing clothianidin.

(15) For plant protection products containing clothianidin, where Member States grant a grace period pursuant to Article 46 of Regulation (EC) No 1107/2009, that period should, at the latest, expire on 19 December 2018.

(16) The prohibition of placing on the market and use of treated seeds should apply only as of 19 December 2018 in order to allow for a sufficient period of transition.

(17) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Plants, Animals, Food and Feed,

HAS ADOPTED THIS REGULATION:

Article 1

Amendment to Implementing Regulation (EU) No 540/2011

Part A of the Annex to Implementing Regulation (EU) No 540/2011 is amended in accordance with the Annex to this Regulation.

Article 2

Prohibition of the placing on the market and use of treated seeds

Seeds treated with plant protection products containing clothianidin shall not be placed on the market or used, except where:

(a) the seeds are intended to be used only in permanent greenhouses, and

(b) the resulting crop stays within a permanent greenhouse during its entire life cycle.

Article 3

Transitional measures

Member States shall, in accordance with Regulation (EC) No 1107/2009, where necessary amend or withdraw existing authorisations for plant protection products containing clothianidin as active substance by 19 September 2018 at the latest.

Article 4

Grace period

Any grace period granted by Member States in accordance with Article 46 of Regulation (EC) No 1107/2009 shall be as short as possible and shall expire by 19 December 2018 at the latest.

Article 5

Amendment to Implementing Regulation (EU) No 485/2013

As regards seeds which have been treated with plant protection products containing clothianidin, Article 2 of Implementing Regulation (EU) No 485/2013 is deleted.

Article 6

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

However, Article 2 and Article 5 shall apply as of 19 December 2018.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 29 May 2018.

For the Commission
The President
Jean-Claude JUNCKER

ANNEX

The text of the column 'Specific provisions' of row 121, clothianidin, of Part A of the Annex to Implementing Regulation (EU) No 540/2011 is replaced by the following:

'PART A

Only uses as insecticide, in permanent greenhouses or for the treatment of seeds intended to be used only in permanent greenhouses, may be authorised. The resulting crop must stay within a permanent greenhouse during its entire life cycle.

PART B

For the implementation of the uniform principles as referred to in Article 29(6) of Regulation (EC) No 1107/2009, the conclusions of the review report on clothianidin, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 27 January 2006 and the conclusions of the revised addendum of the review report on clothianidin as finalised in the Standing Committee on Plants, Animals, Food and Feed on 27 April 2018 shall be taken into account.

In this overall assessment Member States must pay particular attention to:

— the risk to groundwater;

— the risk to bees and bumble bees released for pollination in permanent greenhouses;

— the exposure of bees via the consumption of contaminated water from the permanent greenhouses.

Member States shall ensure that the seed coating shall only be performed in professional seed treatment facilities. Those facilities must apply the best available techniques in order to ensure that the release of dust during application to the seed, storage, and transport can be minimised.

Conditions of use shall include risk mitigation measures, where appropriate.'

COMMISSION IMPLEMENTING REGULATION (EU) 2018/785

of 29 May 2018

amending Implementing Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance thiamethoxam

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC ([1]), and in particular Article 21(3), Article 49(2) and Article 78(2) thereof,

Whereas:

(1) The active substance thiamethoxam was included in Annex I to Council Directive 91/414/EEC ([2]) by Commission Directive 2007/6/EC ([3]).

(2) Active substances included in Annex I to Directive 91/414/EEC are deemed to have been approved under Regulation (EC) No 1107/2009 and are listed in Part A of the Annex to Commission Implementing Regulation (EU) No 540/2011 ([4]).

(3) Commission Implementing Regulation (EU) No 485/2013 ([5]) amended the conditions of approval of the active substance thiamethoxam and required the applicant to provide confirmatory information as regards:

(a) the risk to pollinators other than honey bees;

(b) the risk to honey bees foraging in nectar or pollen in succeeding crops;

(c) the potential uptake via roots to flowering weeds;

(d) the risk to honey bees foraging on insect honey dew;

(e) the potential guttation exposure and the acute and the long-term risk to colony survival and development, and the risk to bee brood resulting from such exposure;

(f) the potential exposure to dust drift following drill and the acute and the long-term risk to colony survival and development, and the risk to bee brood resulting from such exposure;

(g) the acute and long term risk to colony survival and development and the risk to bee brood for honeybees from ingestion of contaminated nectar and pollen.

(4) The applicant submitted additional information concerning bees (i.e. honey bees, bumble bees and solitary bees) to the rapporteur Member State Spain.

(5) Spain assessed the additional information submitted by the applicant. It submitted its assessment, in the form of an addendum to the draft assessment report, to the other Member States, the Commission and the European Food Safety Authority ('the Authority') on 12 November 2015.

([1]) OJ L 309, 24.11.2009, p. 1.
([2]) Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market (OJ L 230, 19.8.1991, p. 1).
([3]) Commission Directive 2007/6/EC of 14 February 2007 amending Council Directive 91/414/EEC to include metrafenone, Bacillus subtilis, spinosad and thiamethoxam as active substances (OJ L 43, 15.2.2007, p. 13).
([4]) Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances (OJ L 153, 11.6.2011, p. 1).
([5]) Commission Implementing Regulation (EU) No 485/2013 of 24 May 2013 amending Implementing Regulation (EU) No 540/2011, as regards the conditions of approval of the active substances clothianidin, thiamethoxam and imidacloprid, and prohibiting the use and sale of seeds treated with plant protection products containing those active substances (OJ L 139, 25.5.2013, p. 12).

(6) The Member States, the applicant and the Authority were consulted and asked to provide comments on the assessment of the rapporteur Member State. The Authority published a Technical Report summarising the outcome of this consultation for thiamethoxam on 20 April 2016 ([1]).

(7) As foreseen in recital (16) of Implementing Regulation (EU) No 485/2013, the Commission initiated a review of new scientific information on 11 February 2015 by mandating EFSA to organise an open call for data. EFSA launched an open call for data which ended on 30 September 2015 ([2]).

(8) On 13 November 2015, the Commission requested EFSA to provide conclusions concerning an updated risk assessment for bees as regards the use of thiamethoxam applied as a seed treatment or granules by organising a peer review and taking into account the data collected in the framework of the specific open call for data and any other new data from studies, research and monitoring activities that are relevant to the uses under consideration. The Authority presented its conclusion on the peer review of the updated pesticide risk assessment for bees for the active substance thiamethoxam considering the uses as seed treatment and granules on 28 February 2018 ([3]). The applicant was given the opportunity to comment on this conclusion. The applicant submitted its comments which have been carefully examined.

(9) The draft assessment report, the addendum, the Technical Report and the conclusion of the Authority were reviewed by the Member States and the Commission within the Standing Committee on Plants, Animals, Food and Feed and finalised on 27 April 2018 in the form of a revised addendum to the Commission review report for thiamethoxam.

(10) The Commission invited the applicant to submit its comments on the revised addendum to the review report for thiamethoxam. The applicant submitted its comments which have been carefully examined.

(11) Having reviewed the information submitted by the applicant, the Commission has concluded that the further confirmatory information required by Implementing Regulation (EU) No 485/2013 has not been provided, and having also considered the conclusion on the updated risk assessment for bees, the Commission has concluded that further risks to bees cannot be excluded without imposing further restrictions. Bearing in mind the need to ensure a level of safety and protection consistent with the high level of protection of animal health that is sought within the Union, it is appropriate to prohibit all outdoor uses. Therefore, it is appropriate to limit the use of thiamethoxam to permanent greenhouses and to require that the resulting crop stays its entire life cycle within a permanent greenhouse, so that it is not replanted outside.

(12) The Annex to Implementing Regulation (EU) No 540/2011 should therefore be amended accordingly.

(13) Taking into account the risks for bees from treated seeds, the placing on the market and the use of seeds treated with plant protection products containing thiamethoxam should be subject to the same restrictions as the use of thiamethoxam. It is therefore appropriate to provide that seeds treated with plant protection products containing thiamethoxam shall not be placed on the market or used, except where the seeds are intended to be used only in permanent greenhouses and the resulting crop stays within a permanent greenhouse during its entire life cycle.

(14) Member States should be allowed sufficient time to amend or withdraw authorisations for plant protection products containing thiamethoxam.

(15) For plant protection products containing thiamethoxam, where Member States grant a grace period pursuant to Article 46 of Regulation (EC) No 1107/2009, that period should, at the latest, expire on 19 December 2018.

([1]) EFSA (European Food Safety Authority), 2016. Technical report on the outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for thiamethoxam in light of confirmatory data. EFSA supporting publication 2016:EN-1020. 27 pp.

([2]) EFSA (European Food Safety Authority), 2015. Technical report on the open call for new scientific information as regards the risk to bees from the use of the three neonicotinoid pesticide active substances clothianidin, imidacloprid and thiamethoxam applied as seed treatments and granules in the EU. EFSA supporting publication 2015:EN-903. 8pp.

([3]) EFSA (European Food Safety Authority), 2018. Conclusions on the peer review of the pesticide risk assessment for bees for the active substance thiamethoxam considering the uses as seed treatments and granules. *EFSA Journal* 2018;16(2):5179, 59 pp.

(16) The prohibition of placing on the market and use of treated seeds should apply only as of 19 December 2018 in order to allow for a sufficient period of transition.

(17) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Plants, Animals, Food and Feed,

HAS ADOPTED THIS REGULATION:

Article 1

Amendment to Implementing Regulation (EU) No 540/2011

Part A of the Annex to Implementing Regulation (EU) No 540/2011 is amended in accordance with the Annex to this Regulation.

Article 2

Prohibition of the placing on the market and use of treated seeds

Seeds treated with plant protection products containing thiamethoxam shall not be placed on the market or used, except where:

(a) the seeds are intended to be used only in permanent greenhouses, and

(b) the resulting crop stays within a permanent greenhouse during its entire life cycle.

Article 3

Transitional measures

Member States shall, in accordance with Regulation (EC) No 1107/2009, where necessary amend or withdraw existing authorisations for plant protection products containing thiamethoxam as active substance by 19 September 2018 at the latest.

Article 4

Grace period

Any grace period granted by Member States in accordance with Article 46 of Regulation (EC) No 1107/2009 shall be as short as possible and shall expire by 19 December 2018 at the latest.

Article 5

Amendment to Implementing Regulation (EU) No 485/2013

As regards seeds which have been treated with plant protection products containing thiamethoxam, Article 2 of Implementing Regulation (EU) No 485/2013 is deleted.

Article 6

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

However, Article 2 and Article 5 shall apply as of 19 December 2018.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 29 May 2018.

For the Commission
The President
Jean-Claude JUNCKER

ANNEX

The text of the column 'Specific provisions' of row 140, thiamethoxam, of Part A of the Annex to Implementing Regulation (EU) No 540/2011 is replaced by the following:

'PART A

Only uses as insecticide, in permanent greenhouses or for the treatment of seeds intended to be used only in permanent greenhouses, may be authorised. The resulting crop must stay within a permanent greenhouse during its entire life cycle.

PART B

For the implementation of the uniform principles as referred to in Article 29(6) of Regulation (EC) No 1107/2009, the conclusions of the review report on thiamethoxam, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 14 July 2006 and the conclusions of the revised addendum of the review report on thiamethoxam as finalised in the Standing Committee on Plants, Animals, Food and Feed on 27 April 2018 shall be taken into account.

In this overall assessment Member States must pay particular attention to:

— the risk to groundwater;

— the risk to aquatic organisms;

— the risk to bees and bumble bees released for pollination in permanent greenhouses;

— the exposure of bees via the consumption of contaminated water from the permanent greenhouses.

Member States shall ensure that the seed coating shall only be performed in professional seed treatment facilities. Those facilities must apply the best available techniques in order to ensure that the release of dust during application to the seed, storage, and transport can be minimised.

Conditions of use shall include risk mitigation measures, where appropriate.'

DECISIONS

COUNCIL DECISION (EU) 2018/786

of 22 May 2018

on the position to be adopted, on behalf of the European Union, within the EEA Joint Committee concerning the amendment of Protocol 31 to the EEA Agreement, on cooperation in specific fields outside the four freedoms (Budget line 04 03 01 03: 'Free movement of workers, co-ordination of social security schemes and measures for migrants including migrants from third countries')

(Text with EEA relevance)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 46 and 48 in conjunction with Article 218(9) thereof,

Having regard to Council Regulation (EC) No 2894/94 of 28 November 1994 concerning arrangements for implementing the Agreement on the European Economic Area ([1]), and in particular Article 1(3) thereof,

Having regard to the proposal from the European Commission,

Whereas:

(1) The Agreement on the European Economic Area ([2]) ('the EEA Agreement') entered into force on 1 January 1994.

(2) Pursuant to Article 98 of the EEA Agreement, the EEA Joint Committee may decide to amend, inter alia, Protocol 31 to the EEA Agreement.

(3) Protocol 31 to the EEA Agreement contains specific provisions on cooperation in specific fields outside the four freedoms.

(4) It is appropriate to continue the cooperation of the Contracting Parties to the EEA Agreement in Union actions funded from the general budget of the Union regarding the free movement of workers, the coordination of social security systems and measures for migrants, including migrants from third countries.

(5) Protocol 31 to the EEA Agreement should therefore be amended in order to allow for that extended cooperation to continue beyond 31 December 2017.

(6) The position of the Union in the EEA Joint Committee should therefore be based on the attached draft decision,

HAS ADOPTED THIS DECISION:

Article 1

The position to be adopted, on behalf of the Union, within the EEA Joint Committee on the proposed amendment of Protocol 31 to the EEA Agreement, on cooperation in specific fields outside the four freedoms, shall be based on the draft decision of the EEA Joint Committee attached to this Decision.

([1]) OJ L 305, 30.11.1994, p. 6.
([2]) OJ L 1, 3.1.1994, p. 3.

Article 2

This Decision shall enter into force on the date of its adoption.

Done at Brussels, 22 May 2018.

For the Council
The President
E. KARANIKOLOV

DRAFT

DECISION OF THE EEA JOINT COMMITTEE No …/2018

of …

amending Protocol 31 to the EEA Agreement, on cooperation in specific fields outside the four freedoms

THE EEA JOINT COMMITTEE,

Having regard to the Agreement on the European Economic Area ('the EEA Agreement'), and in particular Articles 86 and 98 thereof,

Whereas:

(1) It is appropriate to continue the cooperation of the Contracting Parties to the EEA Agreement in Union actions funded from the general budget of the Union regarding the free movement of workers, coordination of social security systems and measures for migrants, including migrants from third countries.

(2) Protocol 31 to the EEA Agreement should therefore be amended in order to allow for that extended cooperation to take place from 1 January 2018,

HAS ADOPTED THIS DECISION:

Article 1

In paragraphs 5 and 13 of Article 5 of Protocol 31 to the EEA Agreement, the words 'and 2017' are replaced by the words ', 2017 and 2018'.

Article 2

This Decision shall enter into force on the day following the last notification under Article 103(1) of the EEA Agreement (*).

It shall apply from 1 January 2018.

Article 3

This Decision shall be published in the EEA Section of, and in the EEA Supplement to, the *Official Journal of the European Union*.

Done at Brussels,

For the EEA Joint Committee

The President *The Secretaries to the EEA Joint Committee*

(*) [No constitutional requirements indicated.] [Constitutional requirements indicated.]

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