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SCIENTIFIC OPINION

Guidance on methodological principles and scientific methods to be taken into account when establishing Reference Points for Action (RPAs) for non-allowed pharmacologically active substances present in food of animal origin[1]

EFSA Panel on Contaminants in the Food Chain (CONTAM)[2, 3]

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ABSTRACT

EFSA was asked by the European Commission to deliver a Scientific Opinion on guidance on methodological principles and scientific methods to be taken into account when establishing Reference Points for Action (RPAs) for non-allowed pharmacologically active substances in food of animal origin. This guidance document presents a simple and pragmatic approach which takes into account both analytical and toxicological considerations. The aim is to define an analytical concentration for a non-allowed pharmacologically active substance that can be determined by official control laboratories and is low enough to adequately protect the consumers of food commodities that contain that substance. The proposed step-wise approach considers factors such as analytical capability, toxic potential and pharmacological activity of the substance in question, and includes the identification of the Reasonably Achievable Lowest Limit of Quantification (RALLOQ), the establishment of a Toxicological Screening Value (TSV) and the derivation of a Toxicologically Based Limit of Quantification (TBLOQ). The TBLOQ is compared with the RALLOQ for the respective substance. If the TBLOQ is equal to or higher than the RALLOQ, then the latter can be accepted as the RPA. If the TBLOQ is lower than the RALLOQ, then the sensitivity of the analytical method needs to be improved. In the case where no further analytical improvements are feasible, a substance-specific risk assessment should be considered. The CONTAM Panel concluded that RPAs should be matrix independent. The CONTAM Panel noted that sometimes non-edible matrices are monitored to identify the administration of non-allowed pharmacologically active substances. In these cases, RPAs cannot be applied. The CONTAM Panel also proposed several criteria where the European Commission might consider it appropriate to consult EFSA for a substance-specific risk assessment.

[1] On request from the European Commission, Question No EFSA-Q-2011-00149, adopted on 22 March 2013.

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KEY WORDS

RPA, TSV, TBLOQ, RALLOQ, non-allowed pharmacologically active substances.

SUMMARY

Following a request from the European Commission, the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) was asked to deliver a Scientific Opinion on guidance on methodological principles and scientific methods to be taken into account when establishing Reference Points for Action (RPAs) for non-allowed pharmacologically active substances used in veterinary medicinal products. According to Regulation (EC) No 470/2009[4], RPAs may be established for non-allowed pharmacologically active substances when it is deemed necessary to ensure the functioning of controls for food of animal origin that is imported or placed on the market. Food of animal origin containing residues of such substances at or above the RPA is considered not to comply with Community legislation. Commission Decision 2002/657/EC[5] requires the use of quality assurance systems and validated methods of analysis and establishes Minimum Required Performance Limits (MRPLs) for analytical methods used for the detection of only a limited number of non-allowed substances (chloramphenicol, nitrofuran metabolites, medroxyprogesterone and malachite green). Currently, these MRPLs are to be used as RPAs when analytical tests are carried out in the framework of residue analyses, irrespective of the matrix tested. So far, RPAs are solely based on analytical considerations and take into account the lowest residue concentration that can be quantified with a validated analytical method. Currently, no consideration is given to the toxic potential of non-allowed pharmacologically active substances when establishing RPAs.

This guidance document presents a simple and pragmatic approach which takes into account both analytical and toxicological considerations when establishing RPAs but this approach does not replace a full risk assessment. When setting an analytical concentration in the context of an RPA, the Reasonably Achievable Lowest Limit of Quantification (RALLOQ) must be identified at which the substance can be measured and confirmed in food of animal origin by official control laboratories using a validated analytical method.

In order to determine whether the RALLOQ for the respective substance is low enough to adequately protect the consumer, consideration of the toxic potential and pharmacological activity of the substance is needed. As the substances of concern are non-allowed and, therefore, have no maximum residue limit (MRL), it is likely that the toxicological information on these substances is limited or includes properties, such as genotoxicity, not considered appropriate for authorised substances.

Substances which are genotoxic are of concern because they may also be carcinogenic or cause germ cell mutations. Based on analysis of the potency of a large number of carcinogens, the EFSA Scientific Committee (SC) has identified a threshold of toxicological concern (TTC) value of 0.0025 µg/kg body weight (b.w.) per day for potentially genotoxic compounds as a level of human exposure that would be of low concern from a public health point of view, provided that compounds designated as high potency carcinogens are excluded (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines). The CONTAM Panel decided to use this TTC value of 0.0025 µg/kg b.w. per day as a Toxicological Screening Value (TSV) for non-allowed pharmacologically active substances for which there is direct evidence of genotoxicity or for which there is an alert for genotoxicity (from structural activity relationships or read across). In addition, the CONTAM Panel concluded that this TSV could also be used for non-allowed pharmacologically active substances for which there is lack of information on genotoxicity, and hence genotoxicity could not be excluded. In these cases, the substances are referred to in this guidance as Group I substances.

Since non-allowed pharmacologically active substances that are not genotoxic could have toxicological properties that might to some extent be comparable with those of allowed substances,

[4] 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. 11-22.

[5] Decision 2002/657/EC of 12 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results. OJ L 221, 17.8.2002, p. 8-36.

the CONTAM Panel assessed the acceptable daily intakes (ADIs) for veterinary pharmacologically active substances published so far by the European Medicines Agency (EMA). In Commission Regulation (EU) No 37/2010[6] these substances are classified therapeutically as: a) agents acting on the nervous system, b) agents acting on the reproductive system, c) anti-infectious agents, d) anti-inflammatory agents, e) antiparasitic agents and f) corticoids. In addition, the EMA has also established ADIs for a group of substances having a pharmacological activity different from the classes mentioned above. This group, designated as 'Other', comprised substances such as analgesics, diuretics and sedatives. The ADIs are based on the no-observed-effect levels (NOELs) that are most relevant for the safety assessment, and take into account the appropriate uncertainty factor. The CONTAM Panel decided to use the 5th percentiles of the ADIs for these substances in setting TSVs. The ADIs for pharmacologically active substances acting on the nervous system and reproductive system and for corticoids were comparable and clearly lower than the ADIs for the other groups. Therefore, these three classes should be treated separately when establishing a TSV. The Panel also noted that the number of substances in these classes is very small (20), indicating that the 5th percentiles are not statistically robust. Therefore, the CONTAM Panel decided to group these three classes together and to use the lowest ADI of 0.0042 µg/kg b.w. per day as the TSV for this group. This TSV applies to substances with pharmacological activity on the nervous system or the reproductive system, or that are corticoids (referred to as Group II in this guidance).

For the remaining classes of non-allowed pharmacologically active substances, and the 'other' non-allowed pharmacologically active substances grouped together, the overall 5th percentile of their ADIs, 0.65 µg/kg b.w. per day, was selected as the TSV. This TSV applies to substances without activities falling in the previous two groups (herein referred to as Group III).

The CONTAM Panel noted that if there is information available that a non-allowed pharmacologically active substance causes blood dyscrasias (such as aplastic anaemia) or allergy or is a high potency carcinogen, TSVs based on the procedure described above may not be sufficiently health protective and such substances are considered to be outside the scope of this guidance document. For such substances a specific risk assessment is required.

The CONTAM Panel considered whether RPAs should be set for different matrices (edible tissues or products). Setting values for all possible substance/matrix combinations was considered impractical, and different values assigned to each combination would give a false impression of precision of the RPA. Therefore, the RPAs should be matrix independent and should take into account the overall intake of food of animal origin.

The concentration in a food which is likely not to be of toxicological concern for the consumer was defined by the CONTAM Panel as the Toxicologically Based Limit of Quantification (TBLOQ). The TBLOQ is derived by dividing the TSV value, expressed in µg/person per day, by the amount of food that is consumed. TSVs are based on the most sensitive relevant effect, which in some instances is an effect arising from acute exposure (e.g. neurotoxicity or developmental effects). Therefore, the CONTAM Panel concluded that it was appropriate to use the acute consumption data in its approach to setting TBLOQs, taking into account the consumption pattern of toddlers (aged 1-3 years), who are likely to be the most highly exposed age group due to their higher food intake per kg body weight, and that of adults. The food with the highest consumption is milk including dairy products; values of 1.5 kg and 2.0 kg per day for toddlers and adults, respectively, were used. The highest consumption of any food item other than milk is for meat including processed meat products; 135 g and 390 g per day for toddlers and adults, respectively. For non-allowed pharmacologically active substances that might be applied to animals producing milk for human consumption, the CONTAM Panel decided that a high consumption figure of 1.5 kg food for toddlers and 2 kg food for adults should be used in the derivation of the TBLOQ. Where a substance for which an RPA is needed will not be used in animals producing milk for human consumption (e.g. malachite green), the Panel decided that meat-based

[6] Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. OJ L 15, 20.1.2010, p. 1-72.

consumption values, rounded up to 0.2 kg and 0.5 kg per day for toddlers and adults, respectively, could be used in the derivation of the TBLOQs. The CONTAM Panel considered use of these consumption values to be sufficiently protective to cover primary and processed products and composite foods containing animal derived ingredients.

For Group I substances, adults would not exceed the TSV of 0.0025 µg/kg b.w. per day at a TBLOQ of 0.075 µg/kg food including dairy products, or 0.30 µg/kg food excluding dairy products. Toddlers would not exceed the TSV of 0.0025 µg/kg b.w. per day at a TBLOQ of 0.020 µg/kg food including dairy products, or 0.15 µg/kg food excluding dairy products. For Group II substances, adults would not exceed the TSV of 0.0042 µg/kg b.w. per day at a TBLOQ of 0.125 µg/kg food including dairy products, or 0.50 µg/kg food excluding dairy products. Toddlers would not exceed the TSV of 0.0042 µg/kg b.w. per day at a TBLOQ of 0.034 µg/kg food including dairy products, or 0.25 µg/kg food excluding dairy products. For Group III substances, adults would not exceed the TSV of 0.65 µg/kg b.w. per day at a TBLOQ of 19.5 µg/kg food including dairy products, or 78 µg/kg food excluding dairy products. Toddlers would not exceed the TSV of 0.65 µg/kg b.w. per day at a TBLOQ of 5.2 µg/kg food including dairy products, or 39 µg/kg food excluding dairy products. The CONTAM Panel stresses that the number of significant figures expressed in the TBLOQs reflects the calculation, and is not intended to imply precision in the presented values.

For the establishment of an RPA, the TBLOQ has to be compared with the RALLOQ for the substance. If the TBLOQ is equal to or higher than the RALLOQ, then the latter can be accepted as the RPA. If the TBLOQ is lower than the RALLOQ, then the sensitivity of the analytical method needs to be improved. In the case where no further analytical improvements are feasible, a substance-specific risk assessment should be considered.

The CONTAM Panel illustrates the applicability and the impact of the proposed methodology to establish RPAs for a number of non-allowed pharmacologically active substances. A need for improvement of the analytical methodology is indicated particularly for substances in Groups I and II.

The CONTAM Panel emphasises that this is a simple and pragmatic approach and this guidance does not replace a full risk assessment. The CONTAM Panel recognizes the uncertainties in deriving the TSVs. Overall, however, it is likely to be a conservative approach.

The CONTAM Panel noted that sometimes non-edible matrices are monitored to identify the administration of non-allowed substances. Such monitoring includes, for example, analysis of shells of shrimps, or monitoring of urine, eyes or hair in livestock animals. In the case of non-edible matrices, RPAs should not be applied, but other tools such as recommended analytical concentrations or MRPLs should be considered.

The CONTAM Panel also identified circumstances where the European Commission might consider it appropriate to consult EFSA for a substance-specific risk assessment; such circumstances might include (i) where application of the proposed methodology results in a TBLOQ that is lower than the RALLOQ and there is little or no possibility of significant improvement in the analytical capability within a short to medium time frame, (ii) substances causing blood dyscrasias (such as aplastic anaemia) or allergy or that are high potency carcinogens, which are outside the scope of this guidance document or (iii) where there is experimental or other evidence that the use of the TSV of 0.0025 µg/kg b.w. per day for Group I may not be adequately health protective.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

I. Historical background

During their lifetime, food-producing animals are treated with veterinary medicinal products (VMPs) to treat or prevent diseases or metabolic disorders. Residues of pharmacologically active substances contained in such VMPs will be present during a certain period following administration.

No VMP may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State[7] or by the centralised procedure[8]. VMPs for food-producing animals (including equidae) may be authorised only on condition that residues of the pharmacologically active substance in foodstuffs produced from treated animals will be harmless to consumers, in accordance with Regulation (EC) No 470/2009[4]. Such substances are listed in Table 1 'Allowed substances' of Regulation (EU) No 37/2010[6]. The use of other pharmacologically active substances in VMPs is not allowed. A specific group of non-allowed substances is the group of 'Prohibited substances', listed in Table 2 of the same Regulation.

On several occasions residues of non-allowed (including prohibited) substances were found in food of animal origin. The origin of these residues was diverse and included intentional use with the aim of treating animals for specific conditions as well as contamination incidents. For some substances, both the treatment of animals and the presence of the substance in the environment can be responsible for the presence of residues in food of animal origin. Residues of such substances are highly undesirable.

Regulation (EC) No 470/2009[4] stipulates that for substances which are not classified as 'allowed substances' in accordance with that Regulation, a reference point for action (RPA) may be established in order to ensure the functioning of controls of food animal origin; food of animal origin containing residues of such substances at or above the RPA is considered not to comply with Community legislation.

However, the setting of RPAs in no way condones the illegal use of non-allowed substances to treat food-producing animals. When residues of such substances are detected below the RPA, the competent authority shall carry out investigations to determine whether there has been illegal administration of a non-allowed pharmacologically active substance and, where relevant, shall apply the penalty provided for.

Where the results of those investigations or analytical tests on products of the same origin show a recurrent pattern indicating a potential problem, the competent authority shall retain a record of the findings and inform the Commission and the other Member States. Where appropriate, the Commission shall submit proposals and, in the case of products of Third Country origin, bring the matter to the attention of the competent authority of the country or countries concerned requesting clarification as to the recurrent presence of such residues.

II. Legislative aspects

II.1. Establishment of maximum residue limits

According to Regulation (EC) No 470/2009[4], any pharmacologically active substance intended for use in the Community in veterinary medicinal products which are to be administered to food-producing animals shall be subject to an opinion of the European Medicines Agency[9] ("the Agency") on the maximum residue limit (MRL), formulated by the Committee for Medicinal Products for Veterinary

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

[8] In accordance with Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. OJ L 136, 30.4.2004, p. 1.

[9] Established by Article 55 of Regulation (EC) No 726/2004.

Use[10] ("the Committee"). This opinion consists of a scientific risk assessment[11] and risk management recommendations.

The MRL is the maximum concentration of a residue of the pharmacologically active substance which may be permitted in food of animal origin. MRLs are established when they are considered necessary for the protection of human health in accordance with generally recognised principles of safety assessment, taking into account toxicological risks, environmental contamination, as well as the microbiological and pharmacological effects of residues. Account is also taken of other scientific assessments of the safety of substances concerned which may have been undertaken by international organisations or scientific bodies established within the Community.

The scientific risk assessment considers the metabolism and depletion of pharmacologically active substances in relevant animal species, the type of residues and the amount thereof that may be ingested by human beings over a lifetime without an appreciable health risk expressed in terms of an acceptable daily intake (ADI). The risk management recommendations are based on the scientific risk assessment and consist of an assessment of, amongst others, whether or not a (provisional) MRL should be established or whether the data provided are not sufficient to allow a safe limit to be identified.

Pharmacologically active substances for which the opinion concludes that no MRL is needed or that a (provisional) MRL should be established will subsequently be classified in Table 1 'Allowed substances' of Regulation (EU) 37/2010[6]. All use of other pharmacologically active substances in VMPs is not allowed. A specific group of the non-allowed substances is the group of 'Prohibited substances', listed in Table 2 of the same Regulation. These are substances for which no MRL could be recommended, because the available data are not sufficient to allow a safe limit to be identified, or because a final conclusion concerning human health with regard to residues of a substance cannot be established given the lack of scientific information.

II.2. Establishment and review of reference points for action

Regulation (EC) No 470/2009 stipulates[12] that RPAs may be established for non-allowed substances when it is deemed necessary to ensure the functioning of controls of food of animal origin imported or placed on the market. The procedure foresees establishment of RPAs and their regular review in the light of new scientific data relating to food safety, and evaluation of the outcome of the investigations and analytical tests in case of confirmed presence below the RPA and technological progress.

The RPAs shall be based on the content of an analyte in a sample, which can be detected and confirmed by official control laboratories[13] with a validated analytical method[5]. When establishing RPAs, the Commission shall be advised on analytical aspects by the relevant EU Reference Laboratory; RPAs should take into account the lowest residue concentration which can be quantified with a validated analytical method.

In order to guarantee a high level of protection of health, the Regulation states that the Commission shall apply a risk assessment based on methodological principles as well as scientific methods in consultation with EFSA (Article 19(3)) and, where appropriate, submit a request to EFSA for a risk assessment as to whether the RPAs are adequate to protect human health (Article 19(2)). In the latter

[10] Established by Article 30 of Regulation (EC) No 726/2004.
[11] Such an assessment is not required in case of decision of the Codex Alimentarius Commission, without objection from the Community Delegation, in favour of a maximum residue limit for a pharmacologically active substance intended for use in a veterinary medicinal product, provided that the scientific data taken into consideration have been made available to the Community Delegation prior to the decision of the Codex Alimentarius Commission (Article 14 (3) (b) of Regulation (EC) No 470/2009).
[12] Title III: Reference points for action.
[13] Designated in accordance with Regulation (EC) No 882/2004 of the European Parliament and of the Council of 29 April 2004 on official controls performed to ensure the verification of compliance with feed and food law, animal health and animal welfare rules. OJ L 191, 28.5.2004, p. 1-59.

case, EFSA shall ensure that the opinion is given to the Commission within 210 days of receipt of the request.

II.3. Maximum residue limits under other EU legislation

The use in agriculture in general or in animal husbandry of certain substances not allowed for use in VMPs under Regulation (EC) No 470/2009[4] can result in residues in products derived from food-producing animals. Such substances include pesticides and feed additives.

In the case of pesticides, Regulation (EC) No 396/2005[14] sets MRLs for pesticides currently or formerly used in agriculture in or outside the EU. Where a pesticide is not specifically mentioned, a general default MRL of 0.01 mg/kg applies.

Maximum residue limits are also established for coccidiostats and histomonostats authorised as feed additives in accordance with the provisions of Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition[15], in particular Article 10 (7) thereof.

Maximum levels of coccidiostats and histomonostats in feeds (referred to as non-target feeds) for which the coccidiostats or histomonostats are not authorised but in which they are present following carry-over as a consequence of production, storage and transport practices have been established by Commission Directive 2009/8/EC of 10 February 2009[16]. Commission Regulation (EC) No 124/2009[17] sets maximum levels for these coccidiostats and histomonostats in food of animal origin present as a consequence of the presence of these substances in non-target feed.

II.4. Currently existing reference points for action

In order to ensure the quality and comparability of the analytical results generated by laboratories approved for official residue control, the Commission has adopted Commission Decision 2002/657/EC[18]. This Decision requires the use of quality assurance systems and validated methods of analysis and establishes minimum required performance limits (MRPLs) for analytical methods used for detecting a limited number of substances (chloramphenicol, nitrofuran metabolites, medroxyprogesterone acetate and malachite green).

By the adoption of Commission Decision 2005/34/EC[19], these MRPLs are to be used as RPAs irrespective of the matrix tested for the purpose of control of residues when analytical tests have been carried out in the framework of import control.

III. Specific background

Residues of non-allowed (including prohibited) substances in food of animal origin are highly undesirable, regardless of the origin. Due to the development of laboratory methods capable of finding

[14] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1-16).
[15] Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p.29-43.
[16] Commission Directive 2009/8/EC of 10 February 2009 amending Annex I to Directive 2002/32/EC of the European Parliament and of the Council as regards maximum levels of unavoidable carry-over of coccidiostats or histomonostats in non-target feed. OJ L 40, 11.2.2009, p. 19-25.
[17] Commission Regulation (EC) No 124/2009 of 10 February 2009 setting maximum levels for the presence of coccidiostats or histomonostats in food resulting from the unavoidable carry-over of these substances in non-target feed. OJ L 40, 11.2.2009, p. 7-11.
[18] Commission Decision 2002/657/EC implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results. OJ L 221, 17.8.2002, p. 8-36.
[19] Commission Decision 2005/34/EC laying down harmonised standards for the testing for certain residues in products of animal origin imported from third countries. OJ L 16, 20.1.2005, p. 61-63.)

residues at ever lower levels and potentially leading to a disturbance of the functioning of the internal market, the European Union has established a harmonised approach by introducing a procedure to establish reference points for action for the control of residues of substances the use of which in veterinary medicinal products is not allowed in the Community. The establishment of reference points for action is justified to ensure the functioning of controls of food of animal origin imported or placed on the market.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Art 29 (1) of Regulation (EC) No 178/2002[20], the European Commission asks the European Food Safety Authority for a scientific opinion.

In particular, the opinion should

- Define the relevant methodological principles and scientific criteria to be taken into account when establishing reference points for action for non-allowed pharmacologically active substances present in food of animal origin for which an MRL is not available or cannot be laid down using other procedures in EU legislation to protect public health;

- Indicate whether reference points for action should differ in function of the matrix tested, and if so, define criteria to be applied;

- Propose criteria in which cases it would be appropriate to submit to EFSA a request for a risk assessment whether reference points for action for specific substances are adequate to protect human health.

[20] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31/1, 1.2.2002, p. 1-24.

ASSESSMENT

1. Introduction

As a result of the treatment of food-producing animals with veterinary medicinal products (VMPs), residues of pharmacologically active substances contained in VMPs can be present in animal products intended for human consumption. In accordance with Regulation (EC) No 470/2009[4], these VMPs may only be placed on the market if the residues in animal products do not pose any harm to the consumer. Pharmacologically active substances fulfilling this condition are classified as 'Allowed substances' in Table 1 of Regulation (EU) No 37/2010[6]. All other pharmacologically active substances are considered as 'non-allowed substances' and a specific subgroup of these non-allowed substances is the group of 'Prohibited substances' which is listed in Table 2 of the same Regulation.

Regulation (EC) No 470/2009[4] also stipulates that for non-allowed pharmacologically active substances a reference point for action (RPA) may be established when it is deemed necessary to ensure official controls for food of animal origin. When residues of such non-allowed substances are detected at or above the RPA, the food is considered not to comply with Community legislation, and should be removed from the market. In current practice, the RPAs take into account the lowest residue concentration that can be quantified with a validated analytical method. Until now, RPAs have only been based on minimum required performance limits (MRPLs), and no consideration has been given to the toxicological profile of non-allowed substances when establishing RPAs.

This guidance document presents a simple and pragmatic approach to deal with residues of non-allowed pharmacologically active substances in food. This approach takes into account both analytical and toxicological considerations in the establishment of RPAs for non-allowed pharmacologically active substances. This guidance document does not replace a full risk assessment.

1.1. Current situation: from Minimum Required Performance Limit (MRPL) to Reference Points for Action (RPA)

In the late 1980s and 1990s, the analysis of non-allowed pharmacologically active substances in products of animal origin was often performed with different limits of detection being applied between Member States (MS) and even within one MS. As a consequence, the results of the investigations were often not comparable leading to an unequal treatment of food producers. Prominent examples are the determination of chloramphenicol and nitrofuran metabolites in shrimps or clenbuterol in calves. In order to ensure the quality and especially the comparability of the analytical results generated by laboratories approved for official residue control, the EU Commission deemed it necessary to set strict requirements for analytical methods to be used for official control purposes. In this respect, the concept of routine methods and reference methods was superseded by a criteria approach, in which performance criteria and procedures for the validation of screening and confirmatory methods were established. The rules for the analytical methods to be used in the testing of official samples taken pursuant to Council Directive 96/23/EC[21] and the common criteria for the interpretation of analytical results of official control laboratories for such samples are specified in Commission Decision of 14 August 2002 implementing Council Directive 96/23/EC[21] concerning the performance of analytical methods and the interpretation of results (Decision 2002/657/EC[5]). As an important tool to ensure a harmonised implementation of Council Directive 96/23/EC[21], the Commission progressively established MRPLs for analytical methods for substances for which no permitted limit has been established and in particular for those substances whose use is not allowed, or is specifically prohibited, in the Community.

[21] Council Directive 96/23/EC of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products and repealing Directives 85/358/EEC and 86/469/EEC and Decision 89/187/EEC and 91/664/EEC. OJ L 125, 23.5.96, p. 10-32.

According to Annex I, point 1.18 of Decision 2002/657/EC[5], 'Minimum required performance limit means minimum content of an analyte in a sample, which at least has to be detected and confirmed. It is intended to harmonise the analytical performance of methods for substances for which no permitted limit has been established.'

At this stage, the MRPLs values were clearly meant as a tool to harmonise the analytical performance of methods applied in the MSs based on the instrumental and methodological capabilities. They were solely driven by the analytical methodology and not based on toxicological considerations and not meant as a reference point for legal actions.

Decision 2002/657/EC[5] lays down MRPLs in various matrices for chloramphenicol, nitrofuran metabolites, medroxyprogesterone acetate and the sum of malachite green and leucomalachite green. The MRPLs were adopted as the standard of performance ensuring effective control of Community legislation when testing samples for the presence of certain non-allowed substances.

However, MRPLs correspond to the average limit above which the detection of a substance or its residues could be construed as methodologically meaningful. With the ongoing improvement of analytical equipment and methodology, a number of samples were identified that showed concentrations of non-allowed substances below the MRPLs. These findings often caused trade problems, because analytical results below and above the MRPLs were treated differently, leading either to acceptance or rejection of food lots, especially concerning imports from Third Countries.

In order to establish a harmonised approach for the control of residues of non-allowed substances in food of animal origin imported into the Community, the Commission enacted Decision 2005/34/EC[19] laying down harmonised standards for the testing for certain residues in products of animal origin imported from Third Countries. This Decision lays down the reference points for action (RPA) for residues of substances for which MRPL values have been established in accordance with Decision 2002/657/EC[5] when analytical tests on imported consignments of products of animal origin confirm the presence of such residues, and the action to be undertaken after such confirmation.

Art. 3.1 of Decision 2005/34/EC[19] stipulates 'Where results of analytical tests are at or above the MRPLs laid down in Decision 2002/657/EC[5], the consignment concerned shall be considered non-compliant with Community legislation'.

Art. 3.5 of Decision 2005/34/EC[19] states:

> Where the results of analytical tests on products are below the MRPLs laid down in Decision 2002/657/EC, the products will not be prohibited from entering the food chain. The competent authority shall retain a record of the findings in case of recurrence. Where the results of analytical tests on products from the same origin show a recurrent pattern indicating a potential problem related to one or several prohibited or unauthorised substances, including for instance the recording of four or more confirmed results below the reference points for action for the same substance in imports from a particular origin within a period of six months, the competent authority shall inform the Commission and the other Member States in the Standing Committee on the Food Chain and Animal Health. The Commission shall bring the matter to the attention of the competent authority of the country or countries of origin and shall make appropriate proposals.

Following this Decision, the analytically driven MRPLs originally derived for harmonization of analytical methods became reference points for action for checking compliance of products imported from Third Countries with EU legislation.

However, this Decision regulated only imports from Third Countries and did not apply to food produced within the Community. As a number of products of animal origin originating from MS were found to contain non-allowed substances below and above the MRPLs, the European Commission and

the MS agreed to apply the approach laid down in Decision 2005/34/EC[19], with the necessary changes, also to food of animal origin produced within the Community. This implies in particular that the MRPLs set according to Commission Decision 2002/657/EC[5] shall also be used as reference points for action. This approach, moreover, means that any detection of substances whose use is not authorised in the Community shall be followed by an investigation into the source of the substance in question and appropriate enforcement measures, in particular aiming at the prevention of recurrence in the case of documented illegal use (SANCO-E.2(04)D/521927).

2. Considerations for a new procedure to establish RPAs according to the framework of Regulation (EC) No 470/2009[4]

The aim of establishing an RPA for non-allowed pharmacologically active substances is to define an analytical concentration in food of animal origin that can be determined by official control laboratories and which is low enough to adequately protect the consumers of food commodities that contain the respective substance. For this purpose, both analytical and toxicological considerations are required, and these considerations can be made independently of each other.

2.1. Analytical considerations

As the RPA will be applied to non-allowed pharmacologically active substances used in animal husbandry, it has to be set at a low level that can unequivocally be determined by official control laboratories. Consequently, information is needed on the performance of the analytical methods applied by the official control laboratories for the confirmatory analysis of the respective substance. The European Union Reference Laboratories (EU-RLs) which are designated in accordance with Regulation (EC) No 882/2004[13] as well as the corresponding National Reference Laboratories (NRLs) have a specific responsibility as these should contribute to a high quality and uniformity of analytical results. The duties and responsibilities of the EU-RLs and NRLs are laid down in Articles 32 and 33 of Regulation (EC) No 882/2004[13]. The EU-RLs and NRLs face a special challenge if 'new' non-allowed pharmacologically active substances have to be determined for the first time, when no validated analytical methods are available for their determination at low levels.

When setting an analytical concentration to be applied in the context of an RPA, it must be based on the Reasonably Achievable Lowest Limit of Quantification (RALLOQ) at which the substance can be measured and confirmed by official control laboratories with a validated analytical method. The performance criteria of the analytical method as laid down in Decision 2002/657/EC[5] should be met.

2.2. Toxicological considerations

In order to determine whether the RALLOQ of the available analytical method is low enough to be likely to be of no health concern for the consumer, consideration of the toxic potential and pharmacological activity of the substance is needed. As the substances of concern are non-allowed, it is likely that the toxicological information on these substances is limited or includes properties, such as genotoxicity, not considered appropriate for authorised substances.

The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) considered the applicability of the concept of Threshold of Toxicological Concern (TTC), which uses Cramer classes (EFSA, 2012a) as the basis for the derivation of Toxicological Screening Values (TSVs) for non-allowed pharmacologically active substances for which a threshold mechanism can be assumed. However, the CONTAM Panel noted that some groups of substances that are the subject of this guidance document (e.g. steroids) are excluded from the TTC approach. In addition, the database underlying the TTC concept only contains a small number of pharmacologically active substances. Therefore, the Panel concluded that the TTC concept, with the use of Cramer classes, is not applicable in a general approach for deriving TSVs for non-allowed pharmacologically active substances in the framework of the establishment of RPAs.

Substances which are genotoxic are of particular concern because they may be also carcinogenic or cause germ cell mutations. The EFSA Scientific Committee (SC) has explored substances with a

structural alert for genotoxicity regarding their possible human health risks (EFSA, 2012a). First, high potency carcinogens that would give the highest calculated risks were identified. Then animal bioassay data on over 500 known genotoxic and non-genotoxic carcinogens were considered. Based on the carcinogenic potency of the substances and by mathematical modeling of risks, a TTC value of 0.0025 µg/kg b.w. per day for a compound which is potentially genotoxic was considered by the SC (EFSA, 2012a) as sufficiently conservative to be used for substances with a structural alert for genotoxicity as a level of human exposure that would be of low concern from a public health point of view, provided that compounds designated as high potency carcinogens are excluded (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines).

The CONTAM Panel decided to use this TTC value of 0.0025 µg/kg b.w. per day as a Toxicological Screening Value (TSV) for non-allowed pharmacologically active substances for which there is direct evidence of genotoxicity or for which there is an alert for genotoxicity (from structural activity relationships or read across). In addition, the CONTAM Panel concluded that this TSV could also be used for non-allowed pharmacologically active substances for which there is lack of information on genotoxicity, and hence genotoxicity could not be excluded. In these cases, the substances are referred to in this guidance as Group I substances.

Since non-allowed pharmacologically active substances that are not genotoxic could have toxicological properties that might to some extent be comparable with those of allowed veterinary pharmacologically active substances, as evaluated by the European Medicines Agency (EMA), the CONTAM Panel assessed the Acceptable Daily Intakes (ADIs) for these substances established by the EMA.

These ADIs are based on the No-Observed-Effect Levels (NOELs) that are most relevant for the safety assessment, taking into account relevant uncertainty factors. Until now, the EMA has published ADIs for 167 veterinary pharmacologically active substances. These substances can be grouped into the following therapeutic classes in accordance with Commission Regulation (EU) No 37/2010[6]:

- agents acting on the nervous system;
- agents acting on the reproductive system;
- anti-infectious agents;
- anti-inflammatory agents;
- antiparasitic agents;
- corticoids.

In addition, EMA also established ADIs for a group of substances having a pharmacological activity different from the classes mentioned above. This group, designated as 'Other' in this guidance document, comprised among others, analgesics, diuretics and sedatives. In accordance with Regulation (EC) No 470/2009[4], for this group of substances it is not necessary for the protection of human health to establish MRLs pursuant to a scientific risk assessment of EMA.

The distributions of ADIs for all 167 veterinary pharmacologically active substances together and separately for the different classes are shown in Figure 1 and in Table 1. It can be seen that the distribution of the ADIs for all 167 substances is wide with a median of 6.6 µg/kg b.w. per day and with a 5th percentile of 0.072 µg/kg b.w. per day. From Figure 1, it is obvious that the ADIs for three classes of pharmacologically active substances, those acting on the nervous or reproductive system and the corticoids, are comparable and clearly lower than the ADIs for the other groups. Therefore, these three classes should be treated separately when establishing a TSV. The Panel also noted that the number of substances in these classes is very small, indicating that the 5th percentiles are not statistically robust, and it therefore concluded that it is not appropriate to use these 5th percentiles as a starting point to establish a TSV. Because of this small number, and since the ADIs for these substances are comparable, the Panel decided to group these three classes and to use the lowest ADI of 0.0042 µg/kg b.w. per day (see Table 1) as the TSV for non-allowed pharmacologically active substances acting on the nervous or reproductive system, or being corticoids (group II).

From Figure 1 it can also be seen that the distribution of the ADIs for substances that are anti-infective, anti-inflammatory and anti-parasitic are comparable. The distribution of the ADIs of the substances in the group 'Other' is different from these three classes, particular at the high end of the range. At the low end, the CONTAM Panel noted two low ADI values for alfacalcidol of 0.002 µg/kg b.w. and for romifidine of 0.05 µg/kg b.w. per day. The EMA concluded that there is no need to establish an MRL for the synthetic vitamin D3 analogue alfacalcidol, used for the prevention of milk fever in dairy cows at the end of pregnancy, as inter alia it is rapidly absorbed, extensively metabolised and completely excreted. For romifidine, a sedative mainly used in horses, the EMA states that the clinical indication renders its use in horses bound for slaughter immediately after treatment to be very unlikely and concludes in its risk assessment that an MRL is not required. Given the clinical indication and toxicokinetic properties of these two substances, the CONTAM Panel concludes that these substances are not representative of the types of non-allowed pharmacologically active substances that might be present as residues in food. Except for alfacalcidol and romifidine, all other (30) ADIs in this particular group of substances are equal to or above 1 µg/kg b.w. per day. The CONTAM Panel also noted that the lowest quartile and the 5th percentile of the ADIs for this group of 'Other' substances, which are the most relevant figures for establishing a TSV, are comparable with those of the anti-infective, anti-inflammatory and anti-parasitic substances. The CONTAM Panel therefore decided to combine these substances together with the 'Other' substances and to use the overall 5th percentile for this combined group of 0.65 µg/kg b.w. per day as the TSV to be used for substances not falling into Groups I or II, referred to as Group III in this guidance.

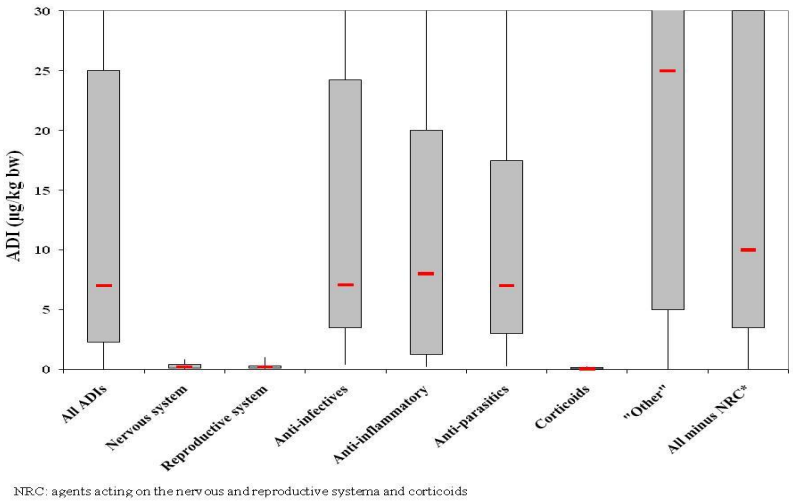

Figure 1: Distribution of acceptable daily intakes (ADIs) established by the European Medicines Agency for 167 allowed veterinary pharmacologically active substances. The boxes in the figure represent the range from the lower to the upper quartile, the red bars indicate the median.

Table 1: The distribution of acceptable daily intake (ADIs) (µg/kg b.w. per day) for different classes of veterinary pharmacologically active substances.

		Acceptable daily intakes (ADI) (µg/kg b.w. per day)							
		Group II[a]			Group III[b]				
	All	Nervous system	Reproductive system	Corticoids	Anti-infective	Anti-inflammatory	Anti-parasitic	'Other'[c]	Group III combined
P5	0.072	n/a	n/a	n/a	1.66	n/a	0.75	0.57	**0.65**
No. of substances	167	4	11	5	52	12	51	32	147
Minimum	0.002	**0.0042**	0.010	0.015	0.40	0.22	0.25	0.002	0.002
Lower quartile	2.0	0.0076	0.073	0.015	3.5	1.25	3.0	5.0	3.48
Median	6.6	0.20	0.20	0.04	7.1	8.0	7.0	25	10
Upper quartile	25	0.43	0.28	0.16	24.3	20	17.5	100	30
Maximum	1650	0.80	1.0	0.20	600	500	420	1 650	1 650

b.w.: body weight; P5: 5th percentile of ADIs expressed as µg/kg b.w. per day; n/a: not applicable due to low numbers.
(a): Group II: substances acting on the nervous system, the reproductive system and corticoids as set in Commission Regulation (EU) No 37/2010[6].
(b): Group III: anti-infective, anti-inflammatory, anti-parasitic substances as set in Commission Regulation (EU) No 37/2010[6] and 'Other' pharmacologically active substances.
(c): Substances for which MRLs are not required in accordance with Regulation (EC) No 470/2009[4].

The CONTAM Panel noted that if there is information available that a non-allowed pharmacologically active substance causes blood dyscrasias (such as aplastic anaemia) or allergy or is a high potency carcinogen, TSVs based on the procedure described above may not be sufficiently health protective and such substances are considered to be outside the scope of this guidance document. For such substances a specific risk assessment is required.

2.3. Matrix and food consumption considerations

2.3.1. RPAs for different matrices.

The CONTAM Panel considered whether RPAs should be set for different matrices (edible tissues or products) based on consumption patterns and tissue distribution characteristics of the non-allowed pharmacologically active substances. Setting values for all possible substance/matrix combinations was considered impractical, and different values assigned to each combination would give a false impression of precision of the RPA. Therefore, the CONTAM Panel concluded that the RPA should be matrix independent and should take into account the overall intake of food of animal origin, assuming that all residue is bioaccessible.

2.3.2. Food consumption considerations

In order to find the concentration in food which is likely not to be of toxicological concern for the consumer, defined by the CONTAM Panel as the Toxicologically Based Limit of Quantification (TBLOQ), the selected TSV, expressed in µg/person per day, has to be divided by the amount of food that is consumed. Because toddlers (i.e. children aged 1-3 years) have the highest food intake per kg body weight and, therefore, are likely the most highly exposed group, consumption by this age group is considered as well as that of adults.

Whilst the body weight of 70 kg for an adult is recommended in the Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data (EFSA, 2012b), the CONTAM Panel has chosen to use a body weight of 60 kg for adults in this guidance document. This was done because the Committee for Medicinal Products for Veterinary Use of the EMA uses a figure of 60 kg in the derivation of ADIs and MRLs for veterinary pharmacologically active substances. A body weight of 12 kg has been used for toddlers in accordance with the Scientific Committee guidance document.

Recently, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) analysed food consumption data from EU Member States and developed default values for consumption of animal origin based on the high intake (95th percentile) of consumers of animal products (EFSA, 2012c). Also in this document a body weight of 60 kg for adults was used. The default high intake values for chronic and acute intake are presented in Table 2.

Table 2: Default values (g/day) for European Union food consumption for high consuming adults and toddlers (EFSA, 2012c).

	Chronic intake[(a)]		Acute intake[(b)]	
	Toddlers[(c)]	**Adults[(d)]**	**Toddlers[(c)]**	**Adults[(d)]**
Meat[(e)]	90	290	135	390
Liver	-	60	-	170
Kidney	-	15	-	100
Animal fat	-	30	-	40
Milk[(f)]	1 050	1 500	1500	2 000
Eggs	35	70	50	130
Honey	-	30	-	50
Fish	65	125	130	280
Seafood	-	75	-	200
Fish + seafood	-	165	-	360

- : No reported values.
(a): Chronic intake is the 95th percentile of the distribution of average individual consumption levels (over the survey period) for consumers only from all available European Union national surveys.
(b): Acute intake is the 95th percentile of the distribution of daily consumption levels (all days considered as independent) for consuming days only from all available European Union national surveys.
(c): Toddlers: 1-3 years of age, 12 kg body weight.
(d): Adults: 18-65 years of age, 60 kg body weight.
(e): Meat including processed meat products.
(f): Milk including dairy products.

TSVs are based on the most sensitive relevant effect, which in some instances is an effect arising from acute exposure (e.g. neurotoxicity or developmental effects). Therefore, the CONTAM Panel concluded that it was appropriate to use the acute consumption data in its approach to deriving TBLOQs. Because of the sporadic nature of exposure to residues of non-allowed pharmacologically active substances, it is unlikely that more than one food containing the same non-allowed pharmacologically active substance would be consumed on the same day. The food with the highest consumption is milk including dairy products; 1.5 kg and 2.0 kg per day for toddlers and adults, respectively (see Table 2). The highest consumption of any food item other than milk is for meat including processed meat products; 135 g and 390 g per day for toddlers and adults, respectively (see Table 2).

For non-allowed pharmacologically active substances that might be applied to animals producing milk for human consumption, the CONTAM Panel decided that a high consumption figure of 1.5 kg food for toddlers and 2 kg food for adults should be used in the derivation of the TBLOQ. Where a substance for which an RPA is needed will not be used in animals producing milk for human consumption (e.g. malachite green), the CONTAM Panel decided that meat-based consumption values, rounded up to 0.2 kg and 0.5 kg per day for toddlers and adults respectively, could be used in the derivation of the TBLOQ.

The CONTAM Panel considered the use of these consumption values sufficiently protective to cover primary and processed products and composite foods containing animal derived ingredients.

2.4. Derivation of Toxicologically-Based Limits of Quantification (TBLOQs)

The TBLOQ is derived by dividing the TSV (expressed on a per person basis) for the different groups of non-allowed pharmacologically active substances by the relevant consumption figure for high level acute consumption by toddlers or by adults (see Table 3).

For Group I substances, adults would not exceed the TSV of 0.0025 µg/kg b.w. per day at a TBLOQ of 0.075 µg/kg food including dairy products, or 0.30 µg/kg food excluding dairy products. Toddlers would not exceed the TSV of 0.0025 µg/kg b.w. per day at a TBLOQ of 0.020 µg/kg food including dairy products, or 0.15 µg/kg food excluding dairy products.

For Group II substances, adults would not exceed the TSV of 0.0042 µg/kg b.w. per day at a TBLOQ of 0.125 µg/kg food including dairy products, or 0.50 µg/kg food excluding dairy products. Toddlers would not exceed the TSV of 0.0042 µg/kg b.w. per day at a TBLOQ of 0.034 µg/kg food including dairy products, or 0.25 µg/kg food excluding dairy products.

For Group III substances, adults would not exceed the TSV of 0.65 µg/kg b.w. per day at a TBLOQ of 19.5 µg/kg food including dairy products, or 78 µg/kg food excluding dairy products. Toddlers would not exceed the TSV of 0.65 µg/kg b.w. per day at a TBLOQ of 5.2 µg/kg food including dairy products, or 39 µg/kg food excluding dairy products.

The CONTAM Panel stresses that the number of significant figures expressed in the TBLOQs reflects the calculation, and is not intended to imply precision in the presented values.

Table 3: Derivation of Toxicologically Based Limits of Quantification (TBLOQ, expressed as µg/kg food) for adults and toddlers based on different food consumption data.

		Adults (60 kg)			Toddlers (12 kg)		
	TSV[(a)]	**TSV[(b)]**	**TBLOQ[(c)] 2 kg food**	**TBLOQ[(c)] 0.5 kg food**	**TSV[(b)]**	**TBLOQ[(c)] 1.5 kg food**	**TBLOQ[(c)] 0.2 kg food**
Group I[(d)]	0.0025	0.15	0.075	0.30	0.030	0.020	0.15
Group II [(e)]	0.0042	0.25	0.125	0.50	0.050	0.034	0.25
Group III[(f)]	0.65	39	19.5	78	7.8	5.2	39

(a): TSV: toxicological screening value expressed as µg/kg b.w. per day.
(b): TSV: toxicological screening value expressed as µg/person per day.
(c): TBLOQ: toxicologically based limits of quantification expressed as µg/kg food.
(d): Group I: substances, except high potency carcinogens, for which genotoxicity cannot be excluded.
(e): Group II: substances acting on the nervous system, the reproductive system and corticoids.
(f): Group III: anti-infective, anti-inflammatory, anti-parasitic substances as set in Commission Regulation (EU) No 37/2010[6] and 'other' non-allowed pharmacologically active substances.

2.5. Monitoring of residues in non-edible matrices

The CONTAM Panel noted that sometimes non-edible matrices are monitored to indicate the administration of non-allowed pharmacologically active substances. Such monitoring includes, for example, analysis of shells of shrimps, or monitoring of urine, eyes and hair of livestock animals. For such matrices, RPAs should not be applied because they are appropriate only for food for human consumption in which residue concentrations may differ from those concentrations in the non-edible matrices. Because of the added value from monitoring of non-edible matrices for identifying exposure of animals to non-allowed pharmacologically active substances, the use of other tools such as recommended analytical concentrations or MRPLs should be considered.

3. Procedure for establishing an RPA

A step-wise approach was developed for the establishment of an RPA for pharmacologically active substances that are not allowed to be used in veterinary medicinal products for food-producing animals, based on the identified RALLOQ and the TBLOQ (Table 3) which is derived from TSVs and food consumption data. Figures 2 and 3 show the decision trees for the assignment of TSVs and for the establishment of RPAs, respectively.

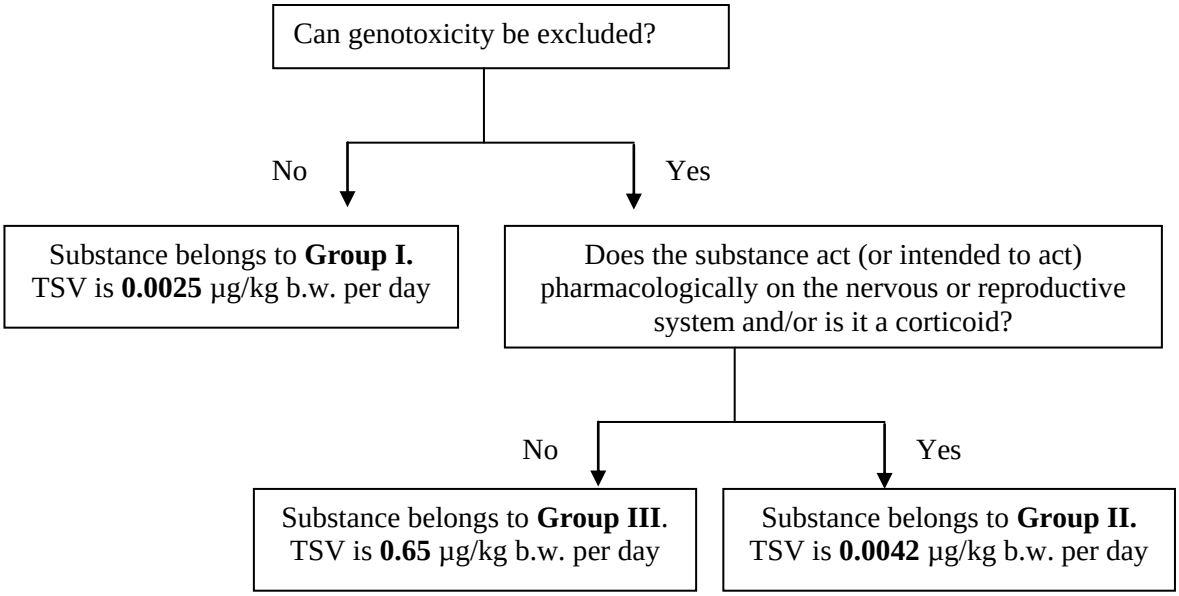

Figure 2: Decision tree for assigning TSVs for non-allowed pharmacologically active substances[22].

When there is no information on genotoxicity of the substance, or, when there is evidence that the substance is genotoxic, a TSV of 0.0025 µg/kg b.w. per day should be used. Evidence for genotoxicity may come from actual genotoxicity data, structural alerts, or read across from related substances. Substances which are genotoxic are of concern because such substances may be also carcinogenic. If the substance belongs to Group II (a substance acting or intended to act pharmacologically on the nervous or reproductive system, or being a corticoid) or to Group III (remaining substances), the respective TSVs are applied.

From the TSV for each group of substances (Group I, II or III), and the food consumption data, the CONTAM Panel has identified four possible TBLOQs depending on (i) whether the substance is used in milk-producing animals or not, and (ii) whether the TBLOQs aim at protecting the adult population or toddlers, which are considered the subpopulation with the highest exposure (see Section 2.4, Table 3). The CONTAM Panel notes that selecting the protection goal is a management decision.

For the establishment of an RPA, the TBLOQ has to be compared with the RALLOQ for the substance. If the TBLOQ is equal to or higher than the RALLOQ, then the latter can be accepted as the RPA. If the TBLOQ is lower than the RALLOQ, then the sensitivity of the analytical method needs to be improved. In the case where no further analytical improvements are feasible within a short to medium time frame, a substance-specific risk assessment should be considered. When, in such a situation, toxicological data for the respective non-allowed pharmacologically active substance is available, these should be taken into consideration.

[22] Substances causing blood dyscrasias (such as aplastic anaemia) or allergy and high potency carcinogens are excluded (see Section 2.2).

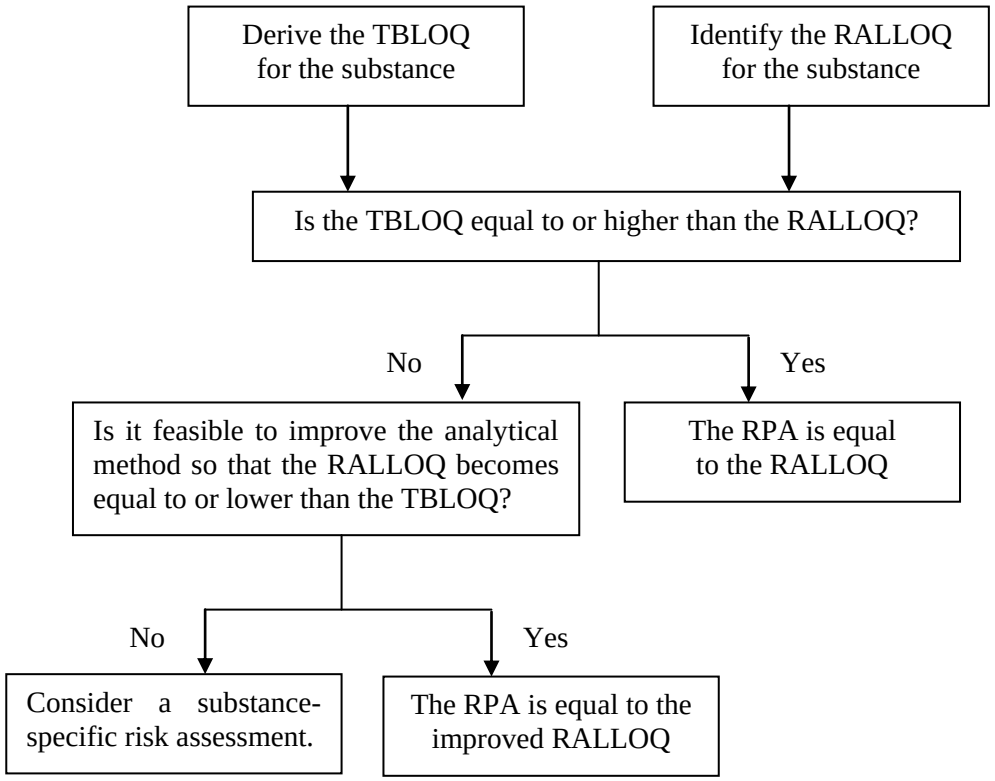

Figure 3: Decision tree for the establishment of an RPA for a non-allowed pharmacologically active substance[22].

4. Illustration of the methodology to establish an RPA

To illustrate the applicability and the impact of the proposed methodology to establish RPAs, the CONTAM Panel selected a number of non-allowed pharmacologically active substances, some of which have been detected in food of animal origin over the past years (Annex I). Based on their classification into one of the 3 groups (Group I, II and III), and on relevant characteristics of the substances (e.g. genotoxicity), a TSV was assigned to each of these substances. Their respective TBLOQs were derived by dividing the TSV (expressed on a per person basis) by the relevant consumption figure for high level acute consumption by toddlers or by adults. At present, RALLOQs are not available. Therefore, the CONTAM Panel compared the different TBLOQs to the MRPLs set in Commission Decision 2002/657/EC[5] and/or to the analytical concentrations recommended for residue monitoring which are currently contained in the CRL Guidance Paper (2007) established by the EU-RLs for residues of veterinary medicinal products in food of animal origin. This illustration is presented in Table 4.

Table 4: Comparison of the TBLOQs with the MRPLs and the currently recommended concentrations for residue monitoring for a selected number of non-allowed pharmacologically active substances.

Substances	TSV[(a)]	Adults (60 kg)			Toddlers (12 kg)			Recommended concentration[(g)] or MRPL
		TSV[(b)]	TBLOQ[(c)] 2 kg food	TBLOQ[(c)] 0.5 kg food	TSV[(b)]	TBLOQ[(c)] 1.5 kg food	TBLOQ[(c)] 0.2 kg food	
Group I[(d)] examples								
Malachite green+Leuco-malachite green	0.0025	0.15	--	0.30	0.030	--	0.15	2.0[(g)]
Metronidazole	0.0025	0.15	0.075	0.30	0.030	0.020	0.15	3.0[(g)]
Carbadox	0.0025	0.15	0.075	0.30	0.030	0.020	0.15	10[(g)]
Group II[(e)] examples								
Mabuterol	0.0042	0.25	0.125	0.50	0.050	0.034	0.25	0.10[(g)](muscle) 0.20[(g)] (liver)
Medroxyproges-terone acetate	0.0042	0.25	0.125	0.50	0.050	0.034	0.25	1.0[(h)]
Zeranol	0.0042	0.25	0.125	0.50	0.050	0.034	0.25	1.0[(g)] (muscle) 2.0[(g)] (liver)
Group III[(f)] examples								
Ibuprofen	0.65	39	19.5	78	7.8	5.2	39	10.0[(g)] (muscle)
Phenylthiouracil	0.65	39	19.5	78	7.8	5.2	39	10.0[(g)] (thyroid)

b.w.: body weight; CRL: Community Reference Laboratory; MRPL: Maximum Required Performance Limit.
(a): TSV: toxicological screening value expressed as µg/kg kg b.w. per day.
(b): TSV: toxicological screening value expressed as µg/person per day.
(c): TBLOQ: toxicologically based limits of quantification expressed as µg/kg food.
(d): Group I: compounds for which genotoxicity cannot be excluded, except high potency carcinogens.
(e): Group II: substances acting on the nervous system, the reproductive system and corticoids
(f): Group III: remaining substances.
(g): Recommended concentrations (expressed as µg/kg per day) (no formal values or MRPLs) provided in CRL Guidance Paper (7 December 2007), CRLs view on state of the art analytical methods for National Residue Control Plans.
(h): adopted as MRPL (expressed as µg/kg) in Decision 2002/657/EC[5].

When comparing the respective TBLOQs to the MRPLs and to the recommended concentrations for residue monitoring currently contained in the CRL Guidance Paper (2007), it can be seen that for the substances phenylthiouracil and ibuprofen the recommended analytical concentration equals most of the respective TBLOQs. The same applies to mabuterol. However, for the other substances, particularly for substances in Groups I and II, the established MRPLs and/or the currently recommended concentrations for residue monitoring are higher than their corresponding TBLOQs, indicating the need for improvement of the analytical methodology for these substances.

The CONTAM Panel emphasises that this is a simple and pragmatic approach and this guidance does not replace a full risk assessment. The CONTAM Panel recognizes the uncertainties in deriving the TSVs. Overall, it is likely to be a conservative approach.

5. Proposed criteria for the European Commission to request EFSA for a risk assessment

In some circumstances, the outcome of the proposed methodology to establish RPAs might indicate that it could be appropriate to submit a request to EFSA for substance-specific risk assessment. Situations when this may be appropriate are:

- Where application of the proposed methodology results in a TBLOQ that is lower than the RALLOQ, and there is little or no possibility of significant improvement in the analytical capability within a short to medium time frame.

- Substances causing blood dyscrasias (such as aplastic anaemia) or allergy or that are high potency carcinogens which are outside the scope of this guidance document.

- Where there is experimental or other evidence that the use of the TSV of 0.0025 µg/kg b.w. per day for Group I substances may not be adequately health protective.

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EFSA Scientific Committee, 2012b. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012;10(3):2579, 32 pp.

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Appendix A. Examples of non-allowed pharmacologically active substances which have been detected in food of animal origin over the past years under the National Residue Control Plans.

Name of the compound	Name of the compound
Acepromazine	Malachite green
Acid Fast Green B	Mapenterol
Azobenzene	Mecarbam
Basic blue 26	Mefenamic acid
Boldenone	Megestrol
Brillant Green	Melengestrol
Bromobuterol	Methylene Blue
Carbadox	Methyltestosterone
Chloramphenicol	Methylthiouracil
Chlorbrombuterol	Methylviolet
Chlormadinone	Metronidazole
Chlormephos	Nandrolone
Chloroform	Naproxen
Chlorpromazine	New methylene blue
Cimaterol	Nile blue
Cimbuterol	Nitenpyram
Clencyclohexerol	Nitrofurans (metabolites AMOZ, AHD, SEM, AOZ)
Clenpenterol	Olaquindox
Clenproperol	Orciprenaline
Colchicine	Oxyphenbutazone
Cristal Violet	Pararosaniline base
Dapsone	Phenylbutazone
Dexamethasone	Propiconazole
Diclofenac	Propiopromazine
Dienestrol	Propylthiouracil
Diethylstilbestrol	Pyrazophos
Dimetridazole	Quinalphos
Erythrosine B	Rhodamine 6G
Ethinyloestradiol	Ritodrin
Ethoprophos	Ronidazole
Ethylviolet	Salbutamol
Fenoterol	Salmeterol
Formothion	Stanozolol
Haloperidol	Tapazole
Hexaconazole	Terbutaline
Hexestrol	Thiouracil
Hydroxymethylclenbuterol	Triazophos
Ibuprofen	Tulobuterol
Isofenphos	Ultramarine
Isofenphos	Zearalanone
Mabuterol	Zeranol

ABREVIATIONS

ADI	Acceptable Daily Intake
b.w.	Body weight
CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
CRL	Community Reference Laboratory
EMA	European Medicines Agency
EU-RL	European Union Reference Laboratory
FEEDAP Panel	EFSA Panel on Additives and Products or Substances used in Animal Feed
MRL	Maximum Residue Limit
MRPL	Minimum Required Performance Limit
MS	Member State
NOEL	No-Observed-Effect Level
NRL	National Reference Laboratory
RALLOQ	Reasonably Achievable Lowest Limit of Quantification
RPA	Reference Point for Action
SC	EFSA Scientific Committee
TBLOQ	Toxicologically Based Limit of Quantification
TSV	Toxicological Screening Value
TTC	Threshold of Toxicological Concern
VMP	Veterinary Medicinal Product