ANSES-Fougeres - EUROPEAN UNION REFERENCE LABORATORY for VMP Residues of Groups A6, B1, B2f, B3e

anses
French agency for food, environmental and occupational health & safety
Investigate, evaluate, protect

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WORK PROGRAMME of the EU-RL for

ANTIMICROBIALS AND DYES

GROUP SUBSTANCES: B1, A6, B2f, B3e

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SUMMARY

INTRODUCTION

The functions and duties of the Reference Laboratory are described in Article 94 of Regulation (EU) No 2017/625 of the European Parliament and of the Council of 15 March 2017 (Official Journal of the European Union L 95, 07.04.2017, pp. 1-142).

Regulation (EU) 625/2017 Art 94(2):
European Union reference laboratories designated in accordance with Article 93(1) shall be responsible for the following tasks insofar as they are included in the reference laboratories' annual or multiannual work programmes that have been established in conformity with the objectives and priorities of the relevant work programmes adopted by the Commission in accordance with Article 36 of Regulation (EU) No 652/2014:
(taking into account Art 147 of (EU) 625/2017)

1 TO ENSURE AVAILABILITY AND USE OF HIGH QUALITY METHODS AND TO ENSURE HIGH QUALITY PERFORMANCE BY NRLs.

Please, provided activities related to Regulation (EU) 2017/625:

- *Art. 94.2.a* ***Providing national reference laboratories with details and guidance on the methods of laboratory analysis, testing or diagnosis, including reference methods.***
  List of EU-RL analytical methods and their SOPs made available through the EU-RL website
- *Art. 94.2.b* ***Providing reference materials to national reference laboratories***
  Production of incurred testing materials, animal experiments, homogeneity testing, stability testing, storage, post-PT testing and shipment during PT and post-PT
- *Art. 94.2.c* ***Coordinating the application by the national reference laboratories and, if necessary, by other official laboratories of the methods referred to in point (a), in particular, by organising regular inter-laboratory comparative testing or proficiency tests and by ensuring appropriate follow-up of such comparative testing or proficiency tests in accordance, where available, with internationally accepted protocols, and informing the Commission and the Member States of the results and follow-up to the inter-laboratory comparative testing or proficiency tests.***
  Providing Proficiency Testing Studies and follow-up of these PTS

- *Art. 94.2.l* ***Where relevant for their area of competence, cooperate among themselves and with the Commission, as appropriate, to develop methods of analysis, testing or diagnosis of high standards.***

Research and Development on future or updated analytical methods for VMPRs

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1.1. Provide NRLs with details and guidance on the methods of laboratory analysis, testing or diagnosis, including reference methods. (a)

Sub-activity 1.1.1. - To provide an updated survey of available EU-NRL network analytical methods

Objectives: To provide an updated survey of available EU-NRL network analytical methods
Description: This survey allows EU-RL and the EU-NRLs network to share a set of information on analytical methods (those for screening and those for confirmation) in use across the EU network and to provide their status in terms of level of validation (A *in-prep* to E *full-valid* levels) and of accreditation (*not accred or under fixed or flexible scopes*)
Expected Output: Report sub-divided in screening methods / confirmatory methods / analytical experts for each method in the NRLs. To be made available to NRLs and DG-SANTE posted onto the EU-RL website *(http://eurl-fougeres-veterinaryresidues.anses.fr)*
Duration: This activity is due to be scheduled once every five years. Last update was released in 2013. Next update to be started in 2018.
EU-RL staff considered for the task: Scientist + Secretary

Sub-activity 1.1.2. - Follow-up and update of the EU-RL Website

Objectives: Follow-up and update of the EU-RL Website
Description: Follow-up and improvement of the EU-RL Website including specific management of the new transfer into the global ANSES-EU-RLs mini-website platform built under the ANSES-format and fully connected to the ANSES-DG public internet system: www.anses.fr - http://eurl-fougeres-veterinaryresidues.anses.fr
Expected Output: Update of webpages and Postage of Documentation for COMM, for NRLs, for Third Country Official Laboratories
Duration: Over the 12 months
EU-RL staff considered for the task: Scientists + Secretary

Sub-activity 1.1.3. – Publications on the public EU-RL website

Objectives: Follow-up and update of the EU-RL Website in regard to analytical method publication
Description: As a follow-up of a recent request from the Commission DG-SANTE, some publication of analytical methods will be posted on the public part of our EU-RL website: http://eurl-fougeres-veterinaryresidues.anses.fr
Expected Output: Provision of information on analytical methods; publication of methods via the EU-RL website (according to the procedure of the pesticide EURLs)
Duration: Over the years
EU-RL staff considered for the task: Scientists + Secretary

1.2. Follow up on requests from NRLs for providing analytical standards. (b)

Sub-activity 1.2.1. - Procurement of reference analytical standards to the network of EU-NRLs

Objectives: Procurement of reference analytical standards to the network of EU-MS-NRLs
Description: All the NRL requests considering standard VMP substances will be investigated but satisfied only according to the commercial availability or non-availability of the substances.
Expected Output: EU-RL list of reference analytical VMP standards and their suppliers/manufacturers will be made available through the EU-RL website (http://eurl-fougeres-veterinaryresidues.anses.fr) (Output 1) and for shipment to the EU-MS NRLs upon their specific request according to our EU-RL website procedure but only for the non-commercially available standards (Output 2)
Duration: Over the 12 months
EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.2.2. - Procurement of reference tissue sample materials to the network of EU-NRLs

Objectives: Procurement of reference sample materials to the network of EU-MS-NRLs
Description: The PT testing materials under convenient and reliable EU-RL storage and subjected to periodic control at EU-RL level will be made available to the NRL-network
Expected Output: EU-RL PT testing materials will be made available through the EU-RL website (http://eurl-fougeres-veterinaryresidues.anses.fr) (Output 1) and for shipment to the EU-MS NRLs upon their specific request through our EU-RL website procedure (Output 2)
Duration: Over the 12 months
EU-RL staff considered for the task: Scientists + Technicians + Secretary

1.3 Organisation of proficiency tests and follow up on the results (c)

1.3.1 Organisation of PTs + 1.3.2 Follow up on and communication of the PT results

Sub-activity 1.3.1.a. / 1.3.2.a. - Provision of Proficiency Testings for Banned substances from Group A6, B2f or B3e (one PT round each year in a different species/matrix each year)

Objectives: Providing to the NRL network under accreditation ISO 17043 one PT including testing for several non-authorised substance residues including their possible metabolites in specific species/products of concern chosen either for their domestic monitoring or for their import control.
Description: As a follow-up of new PT organization launched in 2016-2017, the substances of choice for non-authorized antimicrobial and/or dye substances in 2018 might be again a combination of banned substances chosen among the groups A6, B2f and B3e, i.e. chloramphenicol, nitrofurans, carbadox/olaquindox and/or dyes. But chloramphenicol will be preferred due to the interest in checking EU-NRLs' access to low RPA levels in different matrices. The matrix of choice for the PT materials might be selected from at least one of the different possible species/products (red meat, poultry meat, milk, eggs, honey, and aquaculture species) not excluding on-farm control matrices (urine or drinking water) and with options proposed in relation to the appropriate issues of preceding years. The EU-NRLs method(s) to be controlled will be all considered collectively but the possible 2-step strategy of analysis (screening + confirmation) might be considered for evaluation during this PT round.

Expected Output: Will be delivered by EU-RL to the participants and to DG-SANTE desk officer within the 4 months following the end of the PT round's analyses by EU-NRLs a final report on the results obtained by the participating laboratories (**Output 1**). The report will also be posted in due time on our EU-RL website to the attention of the DG-SANTE exclusively (**Output 2**). A specific follow-up by the EU-RL of corrective actions after non-compliant results will also be undertaken in line with Commission requirements and specific information will be attached to the final report posted to the attention of the DG-SANTE exclusively (**Output 3**) and sent to the Competent Authority (**Output 4**).
Duration: 6 to 8 months for the organisation and delivery of the PT round and final report + 2 to 4 more months for the follow-up of possible corrective actions in some NRLs after final report delivery
EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.3.1.b. / 1.3.2.b. - Provision of Proficiency Testings for Authorized Antimicrobial Substances from Group B1 (one PT round each year in a different species/matrix each year)

Objectives: Providing to the NRL network under accreditation ISO 17043 one PT including testing for several MRL-authorised antimicrobial substance residues including their possible metabolites in specific species/products of concern chosen either for their domestic monitoring or for their import control.
Description: The MRL-based authorised antimicrobials of choice for the 2018 PT should be representative compounds of at least one family of antimicrobials, ie. penicillins, cephalosporins, tetracyclines, aminoglycosides, macrolides, sulfonamides, (fluoro)quinolones, amphenicols, others which are registered in Annex I of Regulation 37/2010/EC. The matrix of choice for the PT materials might be selected from at least one of the different possible species/products (red meat, poultry meat, milk, eggs, honey, and aquaculture species) and with options proposed in relation to the appropriate issues of preceding years. The possible 2-step strategy of analysis (screening + confirmation) might be considered for evaluation during this PT round.
Expected Output: A final report on the results obtained by the participating laboratories will be delivered by the EU-RL to the participants and to DG-SANTE desk officer within the 4 months following the end of the PT round analyses by EU-NRLs (Output 1). The report will also be posted in due time on our EU-RL website to the attention of the DG-SANTE exclusively (Output 2). A specific follow-up by the EU-RL of corrective actions after non-compliant results will also be undertaken in line with Commission requirements and specific information will be attached to the final report posted to the attention of the DG-SANTE exclusively (Output 3) and sent to the Competent Authority (Output 4).
Duration: 6 to 8 months for the organisation and delivery of the PT round and final report + 2 to 4 more months for the follow-up of possible corrective actions in some NRLs after final report delivery
EU-RL staff considered for the task: Scientists + Technicians + Secretary

1.3.3 Preparation of incurred samples

Sub-activity 1.3.3.a. - Production of incurred sample materials for the Proficiency Testing issue and for banned substances from Group A6, B2f or B3e

Objectives: Production of incurred sample materials for the Proficiency Testing task and relevant for banned substances from Group A6, or B2f or B3e
Description: According to the sub-activity 1.3 here-below for testing relevant banned substances from Groups A6 *(CAP, NIFU)* and/or B2f *(CBX, OQX)* and/or B3e (Dyes), the requested reference sample materials (as far as possible being prepared naturally incurred materials) will be produced at the experimental farms of Anses laboratories and prepared in accordance with the standards of PT testing material preparation (homogeneity and stability studies) and under our recognized quality assurance scheme (accreditation N° 1 – 2294 - www.cofrac.fr)
Expected Output: Production of at least 2 new Testing Materials per PT round

Duration: 3 months
EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.3.3.b - Production of incurred sample materials for the Proficiency Testing issue and for authorized antimicrobial substances from Group B1

Objectives: Production of incurred sample materials for the Proficiency Testing task and relevant for MRL authorized antimicrobial substances from Group B1
Description: According to the sub-activity 1.5 here-below for testing relevant MRL authorised antimicrobial substances from Group B1, the requested reference sample materials (as far as possible being prepared naturally incurred materials) will be produced at the experimental farms of Anses laboratories and prepared in accordance with the standards of PT testing material preparation (homogeneity and stability studies) and under our recognised quality assurance scheme (accreditation N° 1 – 2294 - www.cofrac.fr)
Expected Output: Production of at least 2 new Testing Materials per PT round
Duration: 3 months
EU-RL staff considered for the task: Scientists + Technicians + Secretary

1.4 Cooperation collaboration and meetings with other EURLs and scientific exchange (l)

Sub-activity 1.4.1. - Meeting of the cluster of EU-RLs, EU-RLs residues management

Objectives: Meeting with the Commission DG-SANTE and/or with the cluster of EU-RLs for VMPR
Description: Upon the request from or agreement with the Commission DG-SANTE
Expected Output: Up to 3 missions per year for one EU-RL delegate including the annual general meeting of the EU-RLs with mission's report (Outputs 1 – 2 – 3)
Duration: Over 2 days per mission
EU-RL staff considered for the task: Scientists

Sub-activity 1.4.2.– Updating the Decision 657-2002 and the 2 additional guidelines

Objectives: Drafting together with the Cluster of 4 EU-RLs and with the network of NRLs the Technical Guidelines for the validation of performance of VMPR analytical methods that will be updating/replacing those under the current Decision (EC) No 2002/657
Description: As requested from the Commission and from the EU-MS CA expert residue working group on residues of VMPs as of its 23 June 2015 meeting in Brussels, a new Regulation is foreseen to update/replace the Decision (EC) No 2002/657 including all technical guidance for validation of screening and confirmatory VMP residue analytical methods, i.e. Document SANCO/2004/2726 rev4 and CRL Guidelines of 10/1/2010 for validation of the VMPR screening methods. The first draft of this document will be provided under the budget foreseen for 2017. In 2018 additional updates will be made as a follow up to comments from the Commission and the Member States.
Expected Output: Technical Guidelines for Validation of VMPR Analytical Methods complementing the foreseen Regulation for 2018 (Output 1) and posted onto our EU-RL website to the attention of Commission (http://eurl-fougeres-veterinaryresidues.anses.fr) (Output 2)
Duration: Over 12 months
EU-RL staff considered for the task: Scientists

Sub-activity 1.4.3. – Establishment of a common website for the "Residue" EURLs

Objectives: Preparing for a common Internet approach to disseminate VMPR information through the cluster of "EU-RLs"
Description: Discussions will be started during the year within the cluster of VMPR EU-RLs to check technical feasibility for implementing a better coverage of the links toward the EU-RL websites
Expected Output: Building a website portal able to give enough visibility for the different EU-RL website already in place.
Duration: Over the year 2018
EU-RL staff considered for the task: Scientists

Sub-activity 1.4.4. – Harmonisation of proficiency test performance criteria within the "VMPR" EURLs

Objectives: Preparing a common protocol for assessing the PT performance for residue testing through the cluster of "EU-RLs".
Description: Discussions will be started during the year within the cluster of VMPR EU-RLs to try implementing a harmonised approach on PT-Evaluation via an agreed PT-protocol taking into account the individual factors of the EURLs.
Expected Output: Common PT performance criteria.
Duration: Over the year 2018
EU-RL staff considered for the task: Scientists

Sub-activity 1.4.5. – Identification and Quantification of VMP residues down below the MRL at low ppb-level

Objectives: Preparing a common protocol among the cluster of VMPR "EU-RLs" for extending the range of concentration to validate MRL analytical methods down below the MRL at low ppb-level.
Description: Quantitative results for compliant samples below the MRL will need to be submitted to EFSA in the future through the SSD2 in order to allow future risk exposure assessments. The update of the Decision 2002/657 will be part of the legal basis to implement these additional requirements from the COM. Furthermore validation studies of analytical methods for MRL substances should aim to be able to provide also results down to approximately 0.1 x MRL as this is the requirement that forms the current state of discussion with EFSA (provision of sub-MRL results). Anyhow requirements are not fixed and may change along with future revision of Decision 2002/657.
Expected Output: Update of the Decision 2002/657.
Duration: Over the years 2018-2019
EU-RL staff considered for the task: Scientists

1.5 Development and validation of analytical methods (l)

Sub-activity 1.5.1. - Development and Validation of Analytical Methods – An evaluation of the state-of-the-art in EU-MS NRLs analytical instrumentation and of their advanced analytical strategies for a Multi-Antimicrobial Method using suitable LC-HRMS instruments

Objectives: 1 - To demonstrate the current state-of-art of the NRLs network for the use of LC-HRMS instrumentation as screening tool. 2 – To deliver the data raised by a collaborative interlaboratory round for full scan LC-HRMS screening of antimicrobials in spiked meat extracts. 3 – To recommend the criteria of performance for screening of antimicrobial residues in food operated by means of LC-HRMS instruments to update the EU technical guideline for validation of screening/confirmatory VMP residue analytical methods in food.

Description: Considering the advances in mass spectrometric high resolution technologies (i.e. time-of-flight and orbital trap instruments) and the current level of acquisition by EU-MS NRLs of such instruments over the past 5 years, it is now our collective concern to evaluate and to demonstrate the possible future of the analytical strategies to screen and to confirm VMP residues in food by means of this new innovative instrumentation. This study will be implemented as a collaborative study with the aim to strictly assess the LCHRMS instruments' capabilities to be used as reliable screening tools. Extracts spiked with various veterinary medicinal products will be prepared and blindly distributed to the participants to the collaborative study. The analyses will focus on Full Scan MS schemes using if possible the currently 4 different types of HRMS instruments (ToF, Orbitrap, Hybrid-ToF, and Hybrid-Orbitrap). The participants will be authorized to use their own strategy of separative LC conditions. We intend to propose this comparative study at least to the network of EU-MS NRLs but also possibly to selected official laboratories from third Countries. It will be undertaken over a 2-year period. It is intended to produce enough data to assess parameters such as detection capabilities, false-positive rates and false-negative rates for the forthcoming and may be generalising strategies in LC-HRMS screening of VMP residues in food from animal origin. The study will also provide details on the analytical performances of analyses operated by such instrumentation (LC-HRMS) and will further contribute to a set of EU recommendations on criteria dedicated to the evaluation of analytical performance of methods for control (screening / confirmation) by HRMS systems.

Expected Output: Apart from the work already engaged through 2016-2017, the deliveries of the expected outputs have now been revised to also extend to some more 2018 workloads. The following items will be delivered to the network of NRLs the report of the state-of-the-art in LC-HRMS instrumentation in EU by 2018 (Output 1); the report of the collaborative inter-laboratory study by 2018 (Output 2); a set of EU-RL recommendations early 2018 to introduce the HRMS strategies into the regulatory framework including Decision (EC) no 657/2002 (Output 3); these reports will also be presented thoroughly during our EU-RL workshop mid-2018 (Output 4) and also posted onto our EU-RL website to the attention of the network of NRLs (Output 5). A scientific presentation will be delivered in at least one international scientific symposium (Output 6). A publication will be submitted to a peer-reviewed international scientific journal in 2018 (Output 7).

Duration: Over 2017-2018

EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.5.2. - Development and Validation of Analytical Methods – Validation of new or updated confirmatory LC-MS/MS monitoring of beta-lactam residues in meat and/or milk

Objectives: 1 – As a follow-up of the 2017 development and validation of a LC-MS/MS method able to include MRL beta-lactam substances in meat, to develop in 2018 a LC-MS/MS method able to include MRL beta-lactam substances in milk, 2 - To validate the performance of the method in milk in line with the new standardised criteria according to the 2018-foreseen revised of Decision (EC) no 657/2002

Description: Beta-lactam antibiotics are the most important VMP products used in food-producing livestock animals and in milking cows-sheep and goats. Additionally some of them (3rd & 4th generation cephalosporins) are considered critically-important antibiotics in regard to the still-relevant antimicrobial resistance issue.

Therefore, the EU-RL considers the quality of the confirmatory control of these residues in meat and in milk is still to be improved within the EU-MS NRLs network.

Expected Output: To deliver a Standard Operating Procedure in milk presented to the network of NRLs (Output 1 – 2018); a report of validation according to newly revised Decision (EC) no 657/2002 will be drafted (Output 2 – 2018); a hands-on training for beta-lactams in meat and in milk will be delivered during the next annual workshop (Output 3 - 2019); SOPs and validation reports for meat and milk to be posted in due times on our EU-RL website to the attention of the network of NRLs (Output 4 – 2018-2019); a communication to the International Scientific Community to be delivered in a symposium and/or through an international peer-reviewed scientific journal (Output 5 – 2019-2020).

Duration: 2017-2019

EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.5.3. - Development and Validation of Analytical Methods - Extending LC-HRMS screening analysis to all Group B1 antimicrobial residues in different species/products and validating according to new regulations

Objectives: To demonstrate the adaptation and the validation of a full-scan High Resolution analytical method for delivery to field laboratories 1 - for a large scope and high-throughput screening option and 2 – for a confirmatory and quantitative option

Description: The context of the evolution of screening strategies put the new LC-HRMS analytical systems at the first place of advanced technologies dedicated to VMP residue control in balance with the now well-known LC-MS/MS instruments. Considering the network of NRLs and field laboratories in the E.U., the EU-RL considers of high interest to develop and propose to the network a multi-antimicrobial Group B1 method integrating as many antibiotic VMP residues as possible within a single Full Scan High Resolution Mass Spectrometric instrument. This project started mid-2017 after the acquisition of a Q-Exactive+ LC-HRMS equipment and will be extended over the years 2018 and 2019.

Expected Output: In 2018, advances in the development of this HRMS strategy for controlling VMPR in muscle tissue will be presented during the annual workshop of 2018 (Output 1); it will be posted in due times by end 2018 on our EU-RL website to the attention of the network of NRLs (Output 2);

In 2019, a hands-on training dedicated to HRMS strategy (Output 3) together with Standard Operating Procedure (Output 4) will be presented to the network of EU-NRLs during the annual workshop; also a report of validation according to new revised/updated Decision (EC) no 657/2002 to be drafted when the new Regulation/Guidance is adopted (Output 5);

Presentations together with SOP and validation report to be posted in due times over 2018, 2019, 2020 on our EU-RL website to the attention of the network of NRLs (Output 6); communication to the international scientific community to be delivered in a symposium and/or through an international peer-reviewed scientific journal (Output 7).

Duration: Over 2018-2020

EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.5.4. - Development and Validation of Analytical Methods - Enhancing the control for multi-dye residues in aquaculture products by targeted method with LC-MSMS and untargeted approach using LC-HRMS

Objectives: 1 - To release an updated and extended analytical method by LC-MS/MS and/or LC-HRMS for multi-dye residues in aquaculture. 2 – To deliver to the EU-NRLs network and to the scientific community new insights in the metabolomics approach applied to search for dye residue metabolic biomarkers in aquaculture products.

Description: After its ban in 2004 in the EU, the occurrence of malachite green and its leucobase in aquaculture products has been reduced and adequately monitored for several years now. This issue is also well documented in the literature. Recently, the interest in dye residue control was extended to several other dyes

closely related to malachite green, *i.e.* crystal violet and brilliant green. Still possibly used as biocides in aquaculture products imported from other regions of the world, it is also of interest to develop a control strategy able to counteract any attempt of misuse for other chemical substances from the same triarylmethane family (group substitution) or from other related dye families (phenothiazines, xanthenes, phenylazoic dyes, etc...). A project called "Multicolor" was effectively carried out during our "2016-2017" program with primarily the objectives to contribute in developing a multi-dye LC-MSMS method able to extend from our current 5-compound LC-MSMS method and to cover a 10-15+ dye compounds. The outputs of this first phase have been carried out as expected and will be reported in the final activity report of our "2016-2017" program. Additionally, this project included as its second part, a metabolomics approach by LC-HRMS. We evaluated for the first time for this class of compounds how to track possible endogenous or exogenous biomarker(s) of metabolic effects for, at least two dyes, the malachite green and the Victoria pure blue bo, respectively, and by means of *in-vivo* experiments in aquaculture products.

As a follow-up of this previous 2016-2017 project, it is now intended to start reviewing the analytical multi-dye LC-MS/MS method in terms of robustness by transferring it from our current LC-MS/MS system to another more sensitive LC-MS/MS instrument or to a LC-HRMS instrument as well. It is also intended to extend the method to different other aquaculture species of interest in terms of worldwide import control of farmed animals (tilapia, catfish, flat fish, eel, shrimp, prawn, …). A second phase in this 2018-2020 project will be to investigate the presence of metabolites of the Victoria blue family of compounds by comparing and challenging them in *in-vitro* experiments (trout fish microsomes, …) and in *in-vivo* experiments (trout fish species, …).

Expected Output: On the 2016-2017 period were achieved the Outputs of the Multicolor project. This project included a part dedicated to development-validation of a targeted multi-residue method comprising an oxidation step to transform the known leuco-metabolites into their parent form; the procedure was applied to major European concern aquaculture species (trout, salmon, shrimp). Also over this period the 2nd part of the study was dedicated to promote "metabolomics" approach to search for biomarkers after trout treatments with two indicative dyes ("Malachite green" and "Victoria pure blue bo"). The results have been disseminated and promoted with oral presentations at the 2017 Fougeres Workshop and at the 2017 NACRW Conferences (USA), with a SOP posted on the EU-RL website, and with poster presentations at Euroresidue VIII (The Netherlands) and RAFA (Czech Republic). Two scientific publications are also under preparation for submission in 2018.

In 2017 was started a follow-up project named "Metacolor". The first step in this project was to implement an *in vitro* metabolism study of "Victoria pure blue bo" by incubation with trout liver microsomes. Intense and potentially relevant metabolites have been identified.

In 2018, these metabolites will now be compared with those obtained during a second-stage *in vivo* study, which will be extended over 2018 (Output 1). This *in vivo* study will, on the one hand, make it possible to confirm the choice of tracer metabolites compared with the *in-vitro* study and on the other hand to determine the elimination kinetics of Victoria pure blue bo. The strategy and the primary results of the metabolism study approach applied to the Victoria blue family will be also delivered to the network of NRLs during the annual Workshop in 2018 (Output 2).

As a follow-up to advances in the project along the year 2018 and up to 2020, an updated standard operating procedure of the confirmatory LC-MS/MS method for multi-dyes in aquaculture products including extension to new metabolites and/or fish species and a report of validation of the performance of the method will be delivered in 2019 and will be presented at our annual Workshop in 2019 (Output 3). Then the SOP will be also posted on our EU-RL website to the attention of the network of NRLs (Output 4). A communication will be displayed on this issue to the attention of the scientific community during an international symposium dedicated to the veterinary drug residue analysis, namely Euroresidue IX (May 2020) or any other suitable international symposium in the 2019-2020 period (Output 5). Scientific publications will also be submitted to peer-reviewed international journals in relation to the different results of the project in the period 2019-2021 (Output 6).

Duration: Over 2018-2020

EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.5.5. - Development and Validation of Analytical Methods - Validation of new confirmatory LC-MS/MS monitoring of nitrofuran residues in tissues and including the nifursol metabolite

Objectives: 1 – Adaptation to new instrumentation of a LC-MS/MS method capable of monitoring 5 nitrofuran metabolites including the nifursol DNSAH in meat tissues; 2 - To validate the performance of the method in meat in line with the RPA of 1 µg/kg and according to new standardised criteria of the 2018-foreseen revision of Decision (EC) no 657/2002

Description: The current analytical method provided to control nitrofuran banned substances is derived from the method developed in 2002 in a UK-NRL and a NL-NRL and dedicated to 4 metabolites, AOZ, AMOZ, AHD and SEM. Today, there is also an interest to enlarge this control to a 5th nitrofuranic substance called nifursol. Banned since 2005, and previously used as feed additive for chicken and turkey flocks the nifursol is rapidly metabolised in DNSAH. This metabolite could possibly be introduced in a global nitrofuran metabolite method robust and sensitive enough to monitor all 5 nitrofurans at once at the RPA of 1 µg/kg (CCa 0.5 µg/kg). Therefore, the EU-RL considers the development and transfer of such a confirmatory method based on one of its projects published 10 years ago and now to be updated and adapted to the current instrumentation.

Expected Output: The phase of development of the adapted analytical method on a new LC-MS/MS instrument will be started in the 2nd quarter of 2018 followed by its validation process by end of 2018 (Output 1);

In early 2019, a SOP will be prepared for dissemination to the network of NRLs (Output 2); a report of validation according to new revised Decision (EC) no 657/2002 will be drafted (Output 3); SOP and validation report to be posted in due time onto our EU-RL website to the attention of the network of NRLs (Output 4 – 2019); a hands-on training for nitrofuran metabolites in meat will be proposed during the next appropriate annual workshop (Output 5 - 2019); a communication to the international scientific community to be delivered in Symposium and/or through an international peer-reviewed scientific journal (Output 6 – end 2019-2020).

Duration: 2018-2019

EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.5.6. - Development and Validation of Analytical Methods - Confirmatory LC-MS/MS monitoring of colistin residues

Objectives: 1 – Adaptation of a LC-MS/MS method able to monitor the authorised-MRL colistin substance in porcine and in poultry meat first; 2 - To validate the performance of the method in meat in line with the new standardised criteria according to the foreseen revision of Decision (EC) no 657/2002; 3 - To release the analytical method to the network of NRLs; 4 – Adaptation of a LC-MS/MS method able to monitor authorised-MRL colistin substance in porcine and in poultry feed; 5 - To validate the performance of the method in feeds in line with the new standardised criteria according to the foreseen revision of Decision (EC) no 657/2002; 6 - To release the analytical method to the network of NRLs

Description: Colistin is an important VMP product used in food-producing livestock especially in pigs, cattle, sheep, goats, rabbit and in poultry. Additionally it is one of the most critically important antibiotics (CIA) in regard to the still-relevant antimicrobial resistance issue and considering the 2016 Revision 5 of the WHO list of CIAs for human medicine and the current EMA-AMEG list of CIAs in animal husbandry based on degree of risk to humans due to antimicrobial resistance development following use in animals. Therefore, the EU-RL considers of particular interest the quality of the confirmatory control of these residues in meat from food-producing animals and other animal-derived food products and in feed as well. This control is still to be improved within the EU-MS NRLs network. There is an interest to start in 2018 a collaboration with the Cypriot NRL throughout a 3-year project and considering both controls in meat and feed.

Expected Output: In 2018, the collaboration with the Cypriot NRL will be put in place and a specific visit-training in Fougeres will be organized (Output 1).

First analytical developments will be started in SGL-Nicosia in 2018 and also combined in Anses-Fougeres in 2019. It is expected to end up with delivering a SOP in meat and another in feed presented to the network of NRLs by 2020 (Output 2); a report of validation for each of the analytical methods according to new revised

Decision (EC) no 657/2002 will be drafted (Output 3); a hands-on training for colistin in meat and feed to be delivered during the next appropriate annual workshop (Output 4); SOP and validation report to be posted in due times on our EU-RL website to the attention of the network of NRLs (Output 5); a communication to the international scientific community to be delivered in symposium and/or through an international peer-reviewed scientific journal (Output 6).

Duration: 2018-2020

EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.5.7. - Development and Validation of Analytical Methods - Evaluation of innovative technologies for rapid screening of veterinary antimicrobial residues in Foodstuffs - Electrochemical biosensors

Objectives: 1 - Our first action in 2018 will be to go on with the evaluation of both systems here-after described in order to develop new multiplex methods applicable to the screening of multiple banned antibiotics (chloramphenicol, nitrofuran metabolites, dyes) in different matrices (*e.g.* aquaculture products, honey). 2 - The second objective in 2018-2019 will be to develop new multiplex methods applicable to the screening of authorised antibiotics (*e.g.* tetracyclines, sulfonamides, beta-lactams, quinolones) in several matrices (milk, tissues, honey, eggs, etc). This project will allow the comparison of the performances of these 2 electrochemical biosensors, based on the same bioreceptors (eg. antibodies, binding proteins, and aptamers).

Description: Two different electrochemical biosensors have been identified during the programs for 2015 & 2016-2017 which are able to perform multiplex screening of antibiotics:

- A commercial system named Vantix™ (from Vantix Diagnostics™) is a potentiometric biosensor, claimed to provide a reproducible platform on which sensitive and robust assays can be developed. The main advantages of this platform are firstly a reduced investment; secondly each user could perform his own development, using antibodies and antibiotic-enzyme conjugates and thirdly the sample preparation is usually easily manageable (even no preparation for milk). The combs are constituted of 12 channels, which allow the simultaneous analysis of 12 analytes or 12 samples or a mix. The system was evaluated in 2017 to perform the first developments of analytical methods for the specific screening of chloramphenicol residues in milk. The objective in 2018-2019 will be to go on with the development of new methods for a multi-residue screening of authorised substances (eg. tetracyclines, quinolones, sulfonamides, aminoglycosides, macrolides) in milk, honey, tissues (including aquaculture products) and eggs for example and for the screening of multiple banned antibiotics (*e.g.* chloramphenicol, nitrofuran metabolites, dyes) in different matrices (eg. aquaculture products, honey).
- An amperometric biosensor has been developed by a Spanish research team. Their research interests focus on analytical electrochemistry, nanostructured electrochemical interfaces and electrochemical and piezoelectric sensors and biosensors. The multiplexed detection relies on the use of a mixture of target-specific modified magnetic beads and application of direct competitive assays using horseradish peroxidase (HRP)-labelled tracers. The cost of the amperometric biosensor is low. Moreover, the development of methods is manageable, using antibodies and antibiotic-enzyme conjugates. Finally, sample preparation time can be much reduced. In 2017, a technical evaluation of the system was performed in our laboratory. The development of specific method for chloramphenicol detection in milk started in 2017. The objective in the 2018-2019 period will be to go on and enlarge with the development of new methods for a multi-residue screening of authorized substances (*e.g.* tetracyclines, quinolones, sulfonamides, aminoglycosides, macrolides) in milk, honey, tissues (including aquaculture products) and eggs for instance and for the screening of multiple banned antimicrobials (*e.g.* chloramphenicol, nitrofuran metabolites, dyes) in different matrices (*e.g.* aquaculture products, honey).

Expected Output: An intermediate report of the advances in the project will be delivered by end of 2018 (Output 1). It will contain the advances on a single compound method for a banned substance (chloramphenicol) that will be developed and validated in 2018. A presentation of the advances on the Vantix project will be delivered during the EU-RL workshop of 2018 (Output 2) and during an international congress in 2018 (Output 3).

In 2019, a multiplex method for several banned substances will be developed and validated. Two evaluation reports will be delivered by the end of 2019 to the network of NRLs considering the 2 biosensors tested (Output 4). The evaluation reports will be then posted on our EU-RL website to the attention of the network of

NRLs (Output 5). A formal presentation of the final advances on the project will be delivered during the workshop organised in 2019 to the attention of the NRLs experts (Output 6). Then publications in peer-reviewed scientific journals might be also considered (Output 7).
Duration: 2018-2019
EU-RL staff considered for the task: Scientists + Technicians + Secretary

Sub-activity 1.5.8. - Development and Validation of Analytical Methods - Validation of 4 ELISA kit for the screening of nitrofuran metabolites (AOZ, AMOZ, SEM and AHD) in aquaculture products (Supplier Europroxima, The Netherlands): to be compared with the results of ELISA kits validation performed in 2017 with 2 other manufacturers

Objectives: 1 - Evaluation of the performance of 4 commercially available ELISA kits (Europroxima, The Netherlands) aimed at screening of the nitrofuran metabolites in aquaculture products and 2 - comparison with the results of ELISA kits validation performed in 2016 with one other manufacturer (r-Biopharm, Germany) and with the results of the validation of one chemiluminescence immunobiosensor aimed at screening the nitrofuran substances in aquaculture products in 2019.
Description: The screening of nitrofuran metabolites with immunoassays is an interesting alternative to LC-MS/MS methods because of a lower investment in equipment. In 2016, the evaluation of the performance of 4 commercially available kits from r-Biopharm (Germany) was performed. Each ELISA kit targets a single nitrofuran metabolite. Therefore 4 ELISA kits have to be used in parallel to screen the 4 metabolites. These kits will be evaluated according to the decision EC/2002/657 and to the European guideline for the validation of screening methods (2010).
Furthermore the performance of these 4 ELISA kits (from Europroxima, The Netherlands) could be compared to the performance of the 4 kits from the other manufacturer (r-Biopharm) evaluated in 2016, and to the multiplex approach for the screening of nitrofuran metabolite in aquaculture products (chemiluminescence biosensor in 2019).
Expected Output: One evaluation report per kit will be delivered by the end of 2018 to the network of NRLs (Output 1). The evaluation reports will then be posted on our EU-RL website to the attention of the network of NRLs (Output 2). A formal presentation of the advances on the project will be offered to the attention of the NRL experts either during the workshop organised in 2018 or in 2019 (Output 3). A scientific publication in a peer-reviewed journal might be also further considered (Output 4).
Duration: 2018
EU-RL staff considered for the task: Scientists + Technicians + Secretary

1.6 Analysis of official samples (b)

Sub-activity 1.6.1. - ANALYSIS OF OFFICIAL SAMPLES in case of dispute or as third-part evaluation

Objectives: As EU-RL, the ANSES-Fougères will continue with analysing at a reference status or after disputes some of the official samples coming from the NRLs and on their specific demand.
Description: The specific requests arising from certain NRLs to analyse in their place a part or all of the confirmatory sets of samples coming from their National Residue Monitoring Plan especially for confirmation of Group B1 compounds will not be accepted as this kind of workload is neither a priority in EU-RL activities nor a specific EU-RL task requested by the Regulation (EU) 625/2017 and the Annex V of the Directive (EC) 96/23.
Expected Output: From 2 and up to 10 different requests may be considered
Duration: Requests' admissibility/acceptability evaluated and analysis carried out within 1 month
EU-RL staff considered for the task: Scientist + Technicians + Secretary

2 TO PROVIDE SCIENTIFIC AND TECHNICAL ASSISTANCE TO NRLs

Please, provided activities related to Regulation (EU) 2017/625:

- *Art. 94.2.d* ***Coordinating practical arrangements necessary to apply new methods of laboratory analysis, testing or diagnosis, and informing national reference laboratories of advances in this field.***
  GLOBAL TRAININGS DURING ANNUAL WORKSHOPS – ANALYSIS OF OFFICIAL SAMPLES

- *Art. 94.2.e* ***Conducting training courses for staff from national reference laboratories and, if needed, from other official laboratories, as well as of experts from third countries.***
  SPECIFIC ANALYTICAL TRAININGS ON-SITE or at EU-RL FACILITIES
- *Art. 94.2.g* ***Providing information on relevant national, Union and international research activities to national reference laboratories.***
  ANNUAL WORKSHOP / INTERNATIONAL SYMPOSIA / EU-RL WEBSITE

2.1 Providing technical and scientific support to NRLs (d)

Sub-activity 2.1.1. – Continuous technical and scientific communication with the network of EU-MS NRLs

Objectives: Delivering upon requests from the EU-MS-NRLs any technical and scientific advices and information related to the field of VMPR groups A6-B1-B2f-B3e
Description: Over the year, a continuous line of communication is carried out by any means like phone call, emails, EU-RL website, ….
Expected Output: Listing of the issues exchanged with the EU-MS NRLs by the continuous line of communication
Duration: Over 12 months
EU-RL staff considered for the task: Scientists + Secretary

2.2 Organisation of workshops (e)

Sub-activity 2.2.1. - Organisation of the annual workshop to the attention of EU-MS NRLs

Objectives: Organisation of the annual workshop to the attention of EU-MS NRLs
Description: A 2-day or 3-day workshop to the attention of the experts from the network of EU-MS NRLs and EU-CC-NRLs in charge of antimicrobial residue control in food will be organised in conformity with requirements of current enforced Regulation (EU) for Union financial aid to the EU reference laboratories. This annual workshop may also include when necessary a technical training session. The venue and a preliminary agenda will be announced at the beginning of the year and prepared according to main regulatory, scientific and technical issues to be exchanged with the EU-MS NRL network.

Expected Output: Announced at the beginning of the year 2018 (Output 1); Postage onto the EU-RL website (Output 2); Release of the programme and list of participants to the workshop (Output 3); Dissemination of all documents delivered during the workshop by posting onto the EU-RL website (Output 4)
Duration: Over 10 months for preparation-dissemination and over a 3-4 day venue
EU-RL staff considered for the task: Scientists + Technicians + Secretary

2.3 Organisation of training courses (e)

Sub-activity 2.3.1. – Analytical support and technical TRAININGS at the specific request of EU-NRLs or Official Laboratories of Candidate Countries

Objectives: 1-week (5 days) training sessions for 4 scientists in activities in EU-NRL or Official Laboratories of EU Candidate Countries
Description: Organisation at EU-RL-ANSES-Fougères of specific training courses toward scientists from Member States and/or EU-Acceding Countries and/or EU-Candidate Countries, only upon request and specific training agenda to be agreed upon between the Parties.
Expected Output: At least 2 separate trainings related to the screening and/or confirmation of antimicrobial or dye residues in meat and/or other relevant products (milk, fish, honey, egg, …) (Outputs 1-2) are foreseen for the year 2018
Duration: Organised on 20 days maximum over the 12 months and in separate sets of 1-week (5-day) for up to 4 persons or 2-week (10-day) max for up to 2 persons
EU-RL staff considered for the task: Scientists + Technicians + Secretary

2.4 Visits of NRLs (d and e)

Sub-activity 2.4.1. - Projection of visits of EU-RL delegates to EU-NRLs from the Member States or from the Candidate Countries

Objectives: Projection of 2 visits of EU-RL delegates to EU-NRLs from the Member States or from EU-Candidate Countries
Description: The EU-RL-delegate visit to specific EU-NRLs is an occasion of privileged bilateral discussion on issues dedicated to the specificities of each NRL. It is part of the strengthening of the EU-MS NRL networking
Expected Output: Final Report of the visits (Output 1) (Output 2)
Duration: Organised for 2 EU-RL delegates and over a 2-5 day mission depending on the number of labs concerned by the NRL activities in the relevant country visited.
EU-RL staff considered for the task: Scientists

2.5 Providing relevant information on national, Union and Int. research activities to NRLs (g)

Sub-activity 2.5.1. – Continuous technical and scientific communication with the network of EU-MS NRLs ***See for Budget under Sub-activity 2.1.1.***

Objectives: Delivering upon requests from the EU-MS-NRLs any technical and scientific advices and information related to the field of VMPR groups A6-B1-B2f-B3e
Description: Over the year, a continuous line of communication is carried out by any means like phone call, emails, EU-RL website, ….

Expected Output: Listing of the issues exchanged with the EU-MS NRLs by the continuous line of communication
Duration: Over 12 months
EU-RL staff considered for the task: Scientists + Secretary

Sub-activity 2.5.2. - International missions of EU-RL delegates in several symposia, seminaries and workshops for enhancing dissemination of scientific information in the field of antibiotic and dye residues in food***See for Budget under Sub-activity 3.3***

Objectives: International missions of EU-RL delegates in several symposia, seminars and workshops for enhancing dissemination of scientific information in the field of antibiotic and dye residues in food
Description: The active participation (organisation, scientific session chairing, oral communication, poster communication) to European/International workshops, seminaries and symposia are of utmost importance to disseminate the EU-RL information and activity. It is the right place to interact externally in our field of food safety control with the network of EU-NRLs.
Expected Output: Several missions are scheduled for the attention of the scientists of the EU-RL and dissemination of information to be released at EU-RL workshops and posted onto the EU-RL website: (http://eurl-fougeres-veterinaryresidues.anses.fr)
Duration: Over the 12 months there are 12 missions scheduled on a 3 to 5 day travel basis each
EU-RL staff considered for the task: Scientists

2.6 Updating and publication of the list of NRLs

Sub-activity 2.6.1. - *Update of the LIST of EU-MS NRLs in Charge of VMPR Control in Food*

Objectives: Follow-up and update of the LIST of EU-MS NRLs in CHARGE of VMPR CONTROL IN FOOD in regard to Groups Substances : A6, B1, B2f, B3e
Description: as a new requirement of Regulation 2017/625, a list of the EU-MS NRLs in charge of VMPR Control in Food from Animal Origin will be established and regularly updated
Expected Output: A 2-year scope updated list with NRLs contact details to be made publicly available and to to the network of NRLs through the EU-RL website (http://eurl-fougeres-veterinaryresidues.anses.fr) (Output 1)
Duration: Over a 3 month exchange
EU-RL Staff considered for the task: Scientist + Secretary

3 TO PROVIDE SCIENTIFIC AND TECHNICAL ASSISTANCE TO THE EUROPEAN COMMISSION AND OTHER ORGANISATIONS

Please, provide activities related to Regulation (EU) 2017/625:

- *Art. 94.2.f* ***Providing scientific and technical assistance to the Commission within the scope of their mission.***
- *Art. 94.2.h* ***Collaborating within the scope of their mission with laboratories in third countries and with the European Food Safety Authority (EFSA), the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC).***

3.1 Technical and scientific assistance to the Commission (f)

Sub-activity 3.1.1. - **Analysis of National residue monitoring plans of the MS (f)**

Objectives: Evaluation of the National Residue Monitoring Plans of the 27/28 Member States in terms of analytical methods in use for VMPR substances of Groups A6 (*CAP, NIFU, DAP*), B1 (*MRL-antimicrobials*), B2f (*CBX, OQX*), B3e (*Dyes*)
Expected Output: Release of a final report to the Commission DG-SANTE and FVO (Output 1) and posted onto our EU-RL website to the attention of Commission (http://eurl-fougeres-veterinaryresidues.anses.fr) (Output 2)
Duration: Over 2 months
EU-RL staff considered for the task: Scientists

Sub-activity 3.1.2. – **Support to the Commission on specific items upon request (f)**

Objectives: To support the requests from the Commission in regard to items like surveys among NRLs or input on analytical methods for certain substances and in line with VMPR substances of Groups A6 (*CAP, NIFU, DAP*), B1 (*MRL-antimicrobials*), B2f (*CBX, OQX*), B3e (*Dyes*)
Expected Output: 2 or 3 requests over the year
Duration: Over the 12 months
EU-RL staff considered for the task: Scientists

3.2 Collaboration with European and international organisations (EFSA, EMA, Eurachem, CEN, ISO, …) and Third Countries (h)

Sub-activity 3.2.1. - *Co-operation with European / International organisations, : DG-SANTE/FVO, EMA, EFSA, EURACHEM, AOACI, FAO-AIEA, ISO, CEN, FIL-IDF, IUPAC, …*

Objectives: Cooperation where relevant issues and requested with DG-SANTE / FVO, DG-Trade, DG-NEAR, EMA, EFSA, EURACHEM, AOACInt, FAO-IAEA, WHO-Codex, ISO, CEN, IDF, IUPAC, …

Description: There is every year several solicitations from the European or International levels requesting our EU-RL expertise
Expected Output: Exchange and release of reports for expertise data or advices delivered to these European or International Food Safety Official Entities
Duration: Over the 12 months
EU-RL Staff considered for the task: Scientist + Secretary

Sub-activity 3.2.2. - Participation to advanced schools for Third Countries Laboratories like SARAF training courses upon request

Objectives: Dissemination of advanced VMPR information to EU-MS and Third Country Official Lab experts.
Description: Participation to advanced schools like SARAF training courses upon request.
Expected Output: From 1 and up to 3 training courses per year
Duration: 2 to 5 h per course
EU-RL staff considered for the task: Scientists

Sub-activity 3.2.3. – Continuous technical and scientific communication with the network of EU-MS NRLs ***See for Budget under Sub-activity 2.1.1.***

Objectives: Delivering upon requests from the EU-MS-NRLs any technical and scientific advices and information related to the field of VMPR groups A6-B1-B2f-B3e
Description: Over the year, a continuous line of communication is carried out by any means like phone call, emails, EU-RL website, ….
Expected Output: Listing of the issues exchanged with the EU-MS NRLs by the continuous line of communication.
Duration: Over 12 months
EU-RL staff considered for the task: Scientists + Secretary

3.3 Participation in symposiums, workshops and seminars for the dissemination of scientific information. (h)

Sub-activity 3.3.1. - International missions of EU-RL delegates in several symposia, seminaries and workshops for enhancing dissemination of scientific information in the field of antibiotic and dye residues in food***See also 2.5.2.***

Objectives: International missions of EU-RL delegates in several symposia, seminars and workshops for enhancing dissemination of scientific information in the field of antibiotic and dye residues in food
Description: The active participation (organisation, scientific session chairing, oral communication, poster communication) to European/International workshops, seminaries and symposia are of utmost importance to disseminate the EU-RL information and activity. It is the right place to interact externally in our field of food safety control with the network of EU-NRLs and with the Official Laboratories of Third Countries worldwide.
Expected Output: Several missions are scheduled for the attention of the scientists of the EU-RL and dissemination of information to be released at EU-RL workshops and posted onto the EU-RL website: (http://eurl-fougeres-veterinaryresidues.anses.fr)
Duration: Over the 12 months there are 12 missions scheduled on a 3 to 5 day travel basis each
EU-RL staff considered for the task: Scientists

3.4 To ensure a sound and efficient management of the EURL/EURC funding cycle.

Sub-activity 3.4.1. - Compilation of provisional programmes, annual reports and cost estimates

Objectives: Documents to be released to the Commission-DG-Santé in due time according to the contracted agreement.

Description: One programme for 2018 including the scientific & technical tasks, a proposed 1-year budget, and proposed performance indicators (PIs) for the proposed tasks. One final report for 2016-2017 program including scientific & technical issues, PIs, and budget execution. One final report for 2018 program including scientific & technical issues, PIs, and budget execution.

Expected Output: By November 2017, the Programme 2018 including scientific & technical tasks, 1-year budget, and PIs (Output 1) + Postage onto the EURL website to the exclusive attention of COMM (Output 2)
By March 2018, the Final Technical report of the programme for period 2016-2017 (Output 3) + Postage onto the EURL website to the exclusive attention of COMM (Output 4)
By March 2019, the Final Technical report of programme 2018 (Output 5) + Postage onto the EURL website to the exclusive attention of COMM (Output 6) (http://eurl-fougeres-veterinaryresidues.anses.fr)

Duration: Over 18 Months

EU-RL staff considered for the task: Scientists + Secretary

4 REAGENTS AND REFERENCE COLLECTIONS

Please, provided activities related to Regulation (EU) 2017/625:

- *Art. 94.2.*j ***Coordinating or performing tests for the verification of the quality of reagents and lots of reagents used for the diagnosis of foodborne, zoonotic or animal diseases and pests of plants.***

- *Art. 94.2.k* ***Where relevant for their area of competence, establishing and maintaining:***
  - ***i. reference collections of pests of plants and/or reference strains of pathogenic agents;*** ***Not concerned***
  - ***ii. reference collections of materials intended to come into contact with food used to calibrate analytical equipment and provide samples thereof to national reference laboratories;*** ***Follow-up of Reference Materials from PTs***
  - ***iii. up-to-date lists of available reference substances and reagents and of manufacturers and suppliers of such substances and reagents.*** ***Follow-up of Reference Analytical Standards***

4.1 Up to date lists of available reference substances and reagents and of manufacturers and suppliers of such substances and reagents (k)

Sub-activity 4.1.1. - Follow-up of the database of the analytical standards

Objectives/Description: Follow-up of the list of the analytical standards commercially made available from authorised suppliers and of the database for the non-commercially available analytical standards proposed at the EU-RL facilities
Expected Output: A yearly updated report on the database of reference antimicrobial standards to be posted to the network of NRLs through the EU-RL website (http://eurl-fougeres-veterinaryresidues.anses.fr)
Duration: Over the year 2018
EU-RL staff considered for the task: Scientist + Secretary

Sub-activity 4.1.2. - Follow-up of the database for the reference materials

Objectives/Description: Follow-up of the database for the reference materials prepared during EU-RL-organised proficiency testing studies and of the list of reference materials made available from authorised suppliers
Expected Output: A yearly updated report on the database of reference antimicrobial materials created starting from our PT materials and to be made available to the network of NRLs through the EU-RL website (**Output 1**). A yearly updated report on the list of marketed antimicrobial reference materials and to be made available to the network of NRLs through the EU-RL website (**Output 2**)
Duration: Over the year 2018
EU-RL staff considered for the task: Scientist + Secretary

5 REQUIREMENTS RELATED TO OTHER LEGISLATION

Please specify applicable legislation:

No activity related to this issue

Sub-activity 5.x *(name of Sub-activity)*

Objectives: Nil
Description: Nil
Expected Output: Nil
Duration: Nil
EU-RL staff considered for the task: Nil

REMARKS

No remark

(if necessary)

WORK PROGRAMME of EURL for

RESIDUES OF VETERINARY DRUGS

PERIOD: 2018

Version 2.0
(date 15/12/2017

CONTACT DETAILS

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SUMMARY

INTRODUCTION

The EUROPEAN UNION REFERENCE LABORATORY FOR RESIDUES OF VETERINARY MEDICINES AND CONTAMINANTS IN FOOD OF ANIMAL ORIGIN (EURL Berlin) with responsibilities for residues of beta-agonists, anthelmintics, non-steroidal anti-inflammatory drugs and anticoccidials including nitroimidazoles (groups of substances: A5-B2a-B2b-B2e) is part of Department 5 “Method Standardisation, Reference Laboratories, Antibiotic Resistance” of the BVL (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit - Federal Office of Consumer Protection and Food Safety).

The analytical activities of the EURL Berlin are pursued by specialised sub-units, which are in charge of the different substance groups within the responsibility of the EURL Berlin. They are supplemented by a sub-unit in charge of the preparation of incurred test materials to be used as in-house reference samples and for proficiency testing.

The activities listed in the following correspond to the duties and operating conditions of EURLs as laid down in Regulation (EC) No. 2017/625, Article 94 (formerly: Article 32 of Regulation (EC) No. 882/2004).

Regulation (EU) 625/2017 Art 94(2):
European Union reference laboratories designated in accordance with Article 93(1) shall be responsible for the following tasks insofar as they are included in the reference laboratories' annual or multiannual work programmes that have been established in conformity with the objectives and priorities of the relevant work programmes adopted by the Commission in accordance with Article 36 of Regulation (EU) No 652/2014:
(taking into account Art 147 of (EU) 625/2017)

1 TO ENSURE AVAILABILITY AND USE OF HIGH QUALITY METHODS AND TO ENSURE HIGH QUALITY PERFORMANCE BY NRLs.

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.a* ***Providing national reference laboratories with details and guidance on the methods of laboratory analysis, testing or diagnosis, including reference methods.***

- *Art. 94.2.b* ***Providing reference materials to national reference laboratories***

- *Art. 94.2.c* ***Coordinating the application by the national reference laboratories and, if necessary, by other official laboratories of the methods referred to in point (a), in particular, by organising regular inter-laboratory comparative testing or proficiency tests and by ensuring appropriate follow-up of such comparative testing or proficiency tests in accordance, where available, with internationally accepted protocols, and informing the Commission and the Member States of the results and follow-up to the inter-laboratory comparative testing or proficiency tests.***

- *Art. 94.2.l* ***Where relevant for their area of competence, cooperate among themselves and with the Commission, as appropriate, to develop methods of analysis, testing or diagnosis of high standards.***

Sub-activity 1.1 *(94.2.a)*

Objectives:
Provision of up-to-date information to NRLs

Description:
Technical, legal and scientific information is provided to NRLs and official routine laboratories as well as to official laboratories from third countries. The information is made available on the internet (FIS-VL – permanently up-dated web portal of the EURL), where all relevant information can be found on validated methods, standard substances, reference materials, workshops, stability studies, and many more. Important current information is distributed to a mailing list (information service per e-mail). Moreover, specific information is provided on request via e-mail and by telephone support.

Expected Output:
Provision of information on analytical methods; publication of methods via the EURL website (following the procedure of the pesticide EURLs); scientific support via e-mail or telephone

Duration:
2018 and ongoing

Sub-activity 1.2 *(Art. 94.2.b)*

Objectives:
Support to NRLs by provision of reference materials (reference standards and matrix reference materials)

Description:
Suitable (pure) reference standards as well as incurred and blank reference materials are the basis of a successful method development, method validation and method performance control. Especially incurred matrix reference materials are essential for a harmonised residue control and comparable results. The EURL already has a large stock of incurred matrix reference materials, which are continuously controlled for stability, as well as standard substances. Nevertheless, several reference materials are still missing, and the need for additional materials, either due to their relevance for residue control or due to NRL requests, is permanently monitored. Moreover, the need for the substitution of already available reference materials due to instabilities is taken into account.

The production of new reference materials is planned according to these considerations as well as with respect to the future use of the materials in proficiency tests and the provision of incurred material to official control laboratories (OCL) for scientific purposes. Furthermore, it is an ongoing task to investigate possible new veterinary drugs, their metabolisation or degradation products.

Additionally, the availability of reference standards as well as of adequate internal – preferably isotopically labelled – standards is evaluated. Reference standards in stock are controlled according to the concept developed in the 2016/17 working period as far as feasible. In addition, we purchase substances, metabolites or internal standards which we presume to be required.

Reference standards ("standard substances") and incurred reference materials are provided to NRLs and official control laboratories in third countries upon request (ordering form developed in 2016/17 and provided to the OCL via the FIS-VL).

Based on the above-mentioned considerations, the following animal studies for the production of incurred matrix materials are planned in 2018 :

Coccidiostats in laying hens / egg (also see 2.1)
Beta-agonists in hair of cows (multi-annual study)
Beta agonists in urine of calves (4 analytes)
Beta-agonists in tissue (1 analyte)
Anthelmintics in fish (continued from 2017; 4 analytes in total)
Treatment with amitraz in combination with other animal studies

The production of the materials includes the treatment of the animals, the collection (if necessary including the slaughtering of the animals) of the materials and a pre-characterisation of the residues.

In addition, the production of reference materials from "raw" incurred sample materials is planned. The production process covers the following steps: dilution of the material if necessary, homogenisation of the material, aliquotation and packaging of test portions, tests on homogeneity and stability (short-term and mid-term), tests on hydrolysis effects (conjugated residues).

The following materials will be produced and characterised:
NSAID in horse muscle (only homogeneity *)
~~Coccidiostats in egg~~
Multi-residues in milk

* Stability testing (short-term and mid-term) for NSAIDs in horse muscle is planned for the next period. Stability analyses in the past revealed that some NSAIDs showed degradation within the first 2 years of storage. Thereafter, they were stable.

Output:
Pre-tested incurred matrix materials for proficiency tests and for scientific purposes; reference materials for NSAIDs in muscle, ~~coccidiostats in egg~~, multi-residues in milk; support to NRLs/RFLs; cooperation with synthesis laboratories; synthesis of new standards; literature reviews on new substances

Duration:
2018 and ongoing

Sub-activity 1.3 *(Art. 94.2.c)*

Objectives:
Organisation and evaluation of proficiency tests and follow-up on results

Description:

The EURL regularly organises 1 - 2 proficiency tests per year with 3 – 4 samples each, covering multiple analytes in different concentrations. The material usually consists of incurred matrix material produced in animal studies and controlled for homogeneity and stability at the EURL.

The evaluation is effected on the basis of a classical z-score (or z_u-score) evaluation and a point-score system. The point-score system includes an overall evaluation of the laboratories' performances with respect to residue control in general based on pre-set requirements (required analytes and required control levels).

Follow-up measures will be carried out - if necessary - in compliance with the Commission draft "Protocol for management of underperformance […]" guideline of 2007. An overview of the performances per laboratory and MS in the past few years was established in 2013/2014 and is up-dated regularly.

For 2018 the following activities are planned:
Multi-analyte screening PT for residues in milk (~ 15 analytes of different substance groups)
~~Preparation of a PT for coccidiostats in eggs (shipment in early 2019)~~

Expected Output:
Final reports on the 2017 PTs (NSAIDS in milk, coccidiostats in muscle)
Short report and final report on the 2018 PT (multi-residues in milk)
~~Preparation of the test material for the first 2019 PT (coccidiostats in eggs)~~
Assessment of the performance of the NRLs
Assignment of values to the obtained reference materials
Follow-up (questionnaire to participants; support by provision of standard substances, materials, methods, training; provision of additional PT material on request; preparation of test material for x-lateral comparisons on request; report to COM and CA on underperformance)

Duration:
2018 / 2019

Sub-activity 1.4 *(Art. 94.2.c)*

Objectives:
Cooperation, collaboration and meetings with other EURLs and scientific exchange

Description:
As a consequence of the EURL evaluation, the Commission stated that EURLs with overlapping or similar responsibilities should agree upon their work more closely. The agreement with the Commission is also indispensable. For this reason at least one meeting of the 4 EURLs for residues and a representative of the European Commission is necessary per year. Moreover, an additional exchange among the EURLs with respect to an agreed strategy, increased efficiency and exploiting synergy effects is required.

For 2018 two specific projects are envisaged:

- *Common PT performance criteria*
Discussion of a harmonised approach on PT evaluation via an agreed PT-protocol taking into account the individual factors of the EURLs

- *Common EURL website*
Checking the technical feasibility of a common website for the residue EURLs and development of a template (contents, responsibilities)

Expected Output:
Internal documents

Duration:
2018 / 2019

Sub-activity 1.5 *(Art. 94.2.a / l)*

Objectives:
Development of analytical methods and validation of analytical methods

Description:
All relevant methods within the scope of the EURL Berlin are available, validated and accredited. Nevertheless, validation activities due to the extension of methods (analytes, matrices), changes in the required fitness for purpose or progress in methods (new techniques, improved efficiency or accuracy) and instrumentation (changes/improvement in instruments) are permanently ongoing.

The transfer of methods to new LC-MS systems and the optimisation potential for sample preparation, enhanced analyte lists and lower decision limits are regularly checked.

In 2018 this concerns the following methods:
~~Anthelmintics in tissue (method extension, optimisation, validation)~~
Acidic NSAIDs in muscle (revalidation)
Multi-screening in milk with HRMS (method development, validation)
Coccidiostats in egg (optimisation, validation)
Beta-agonists in liver (optimisation)
Implementation of amitraz and metabolites in existing methods (new responsibility on request of COM)

Based on the results of studies in earlier working periods (2015-2017), validated methods should be checked with incurred material for hydrolysis effects and for extraction efficiency.
Furthermore, validation studies for MRL substances should aim to deliver results down to approximately 0.1 * MRL, as this is the requirement at the current state of discussion with EFSA (provision of sub-MRL results). Anyhow, the requirements have not yet been fixed and may change.

Expected Output:
Method descriptions, validation reports

Duration:
2018

Sub-activity 1.6 *(Art. 94.2. l)*

Objectives:
Analysis of official samples

Description:
Official samples will be analysed on request in cases of disputes between MS.

Expected Output:
Provision of definite results in cases of disputes between MS

Duration:
2018 and ongoing

2 TO PROVIDE SCIENTIFIC AND TECHNICAL ASSISTANCE TO NRLs

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.d* ***Coordinating practical arrangements necessary to apply new methods of laboratory analysis, testing or diagnosis, and informing national reference laboratories of advances in this field.***
-
- *Art. 94.2.e* ***Conducting training courses for staff from national reference laboratories and, if needed, from other official laboratories, as well as of experts from third countries.***
-
- *Art. 94.2.g* ***Providing information on relevant national, Union and international research activities to national reference laboratories.***

Sub-activity 2.1 *(Art. 94.2.d /g)*

Objectives:
Provision of technical and scientific support to NRLs

Description:

Assistance to NRLs and other official laboratories for the strengthening and harmonisation of residue control (methods, SOPs, QA, QC, validation, legislation, specific practical or theoretical training, PT follow-up) is provided upon request (also see 2.3). In cases of serious underperformance, e.g. in proficiency tests, the EURL also offers a training.

Additional support to NRLs in the form of confirmatory analyses of questionable samples is provided upon request.

Expected Output:
Provision of information on analytical methods; strengthening of official control; improved food safety

Duration:
2018 and ongoing

Sub-activity 2.2 *(Art. 94.2.g / Art. 94.2.d+e)*

Objectives:

Workshop for scientific exchange, dissemination of information and harmonisation of residue control

Description:
An EURL workshop will be organised in 2018. The following subjects (among others) will be covered:

- Discussions on revision of Decision 2002/657/EC
- New instruments and method developments
- Importance of sample preparation (conjugated residues, extraction)
- Evaluation of Proficiency Tests and follow-ups
- Stability testing in matrix and in solution
- QA measures
- NRCP evaluation and information on substance groups
- Presentations by the NRLs
- Practical training
- Topics according to suggestions by NRLs (collected in surveys conducted at the end of the workshops, or specific topics asked for in additional queries)

The evaluation of the annual EURL work programme as well as the forthcoming work programme will be treated and further specific questions will be discussed depending on the needs of the participants.

Expected Output:
Scientific exchange, workshop report

Duration:
2018 and ongoing : annually 2-3 days

Sub-activity 2.3 *(• Art. 94.2.a / d /e)*

Objectives:
Organisation of training, provision of suitable methods, support in implementation and comprehensive validation

Description:
- *Training courses for strengthening and harmonisation of residue control*

Information on methods, SOPs, QA, QC, validation, legislation as well as specific practical or theoretical training are provided upon request to NRLs and official routine control laboratories (also see 2.1). In cases of serious underperformance, e.g. in proficiency tests, the EURL also offers a training.

A practical training is always part of the annual workshop. Additional individual trainings are agreed at short notice with the NRLs in the framework of the EURL's possibilities and capacities (on average provision of in total 10 working days of training per year).

For 2018 a training for an expert from Croatia has been planned so far.

Expected Output:
Training upon request; provision of information on analytical methods; strengthening of official control; improved food safety

- *Harmonisation of residue control for ß-agonists*
In the 2015/16 work programme, a common method for the determination of acidic and basic NSAIDs in milk was developed, transferred to a new and more sensitive mass spectrometer and submitted to an in-house validation. Due to the interest of several NRLs in the implementation of this method, the milk method was, in addition to the in-house validation, validated in a collaborative study based on an orthogonal experimental design plan. The concept for this kind of validation was developed by the BVL and Quo data, successfully tested on the national level and then successfully transferred to an international level.

The NRLs expressed their interest in participating in this kind of studies also in future, especially beta-agonist detection was of interest. Hence for the period of 2018/2019, a respective study for the determination of beta-agonists in liver shall be organised.

Prior to the validation study, an introduction into the validation approach and a method demonstration are planned in the form of a two-day training for interested participants from the NRLs (limited number of participants). Afterwards, the method shall be transferred to the NRLs and pre-tested before the start of the validation study.

The expected benefits are multiple: for the participating NRLs, a complete in-house validation study is performed, and for the method itself, robust method performance characteristics are determined. This means that a contribution to a harmonised residue control in the EU in form of a comprehensive multi-method for beta-agonists (according to Art. 34 (2)a of Regulation 2017/625/EC) is achieved .

Expected Output:
2018: Information of the NRLs and training; control of successful transfer of the methods; preparation of the validation study
2019: Implementation of the study and evaluation of the results (individual and summary validation reports); final description of a comprehensively validated method for the determination of beta-agonists in liver and publication of the method

Duration:
2018 / 2019 (2019 ongoing with additional methods)

Sub-activity 2.4 *(Art. 94.2.g / Art. 94.2.d+e)*

Objectives:
Supporting visits to NRLs

Description:
In general, one to two European MS NRLs per year are visited after consultation with the Commission on necessity. Scientific information and technical support in the form of methods, SOPs etc. and/or a specific training (practical or theoretical) are provided, and specific problems like underperformance in PTs, QA, QC, validation, legislation etc. are discussed.

For 2018 visits in SK and FI are envisaged.

Expected Output:
NRL-visit reports

Duration:
2018 (2-3 days per visit / depending on requests and performance in PTs)

Sub-activity 2.5 *(Art. 94.2. d / g)*

Objectives:
Provision of information on new developments and relevant research activities to NRLs

Description:
The EURL routinely evaluates the need for additional information with respect to an improvement and a harmonisation of food control. Based on the suggestions of NRLs and third countries as well as on surveys on our own market and of scientific literature, specific research and study activities are started.

For 2018 the following projects are planned:

- *Development of an online validation tool (multi-annual)*
CD 2002/657/EC offers the possibility of an efficient matrix-comprehensive validation using experimental design plans. Since this approach requires some experience, laboratories often avoid the application of this approach and use the less efficient and less robust classical validation approach instead. Given that many NRLs expressed their interest in the availability and use of a validation tool, this project shall be realised in order to support the NRLs, to harmonise validation procedures and for the sake of scientific progress.

In 2018 a feasibility study will be started. Functional and requirement specifications shall be developed together with interested NRLs. Procedures for the use of this tool will be drafted and the implementation for the next working period will be planned (based on the outcome of the feasibility study).

- *Survey on salicylic acid residues in milk (2018)*
Salicylic acid residues are often present in milk samples collected and analysed in the framework of the NRCPs. These residues can be above the MRL of 9 µg/kg, even though a treatment with this drug was unlikely and not indicated. Hence the residues probably originate from a natural background (e.g. feeding conditions). In order to get an overview of possible residue levels in milk of untreated animals, a larger number of samples (50 – 100) from different farms and origins is to be analysed.
Since the analysis has not yet been established in all NRLs and in order to obtain comparable data, the analysis shall be carried out at the EURL. NRLs and German OCL will be contacted and asked for the provision of left-over NRCP samples in order to perform the additional analyses.

- *Residue levels in eggs after treatment of hens (2018)*
Started pullets can be legally treated with coccidiostats, which are not allowed for use in laying hens. It was reported by OCLs that – depending on the time span between the treatment of started pullets and the first production of eggs – elevated residue levels in eggs can occur after a legal treatment of the hens.
This finding shall be verified. The animal study described in sub-activity 1.2 is designed with regard to this issue. Egg samples from this study will be analysed and the data will be evaluated.

Expected Output:
Feasibility study for an on-line validation tool; information on natural residue levels of salicylic acid in milk; residue levels of coccidiostats in eggs after legal treatment of pullets

Duration:
2018 and ongoing

3 TO PROVIDE SCIENTIFIC AND TECHNICAL ASSISTANCE TO THE EUROPEAN COMMISSION AND OTHER ORGANISATIONS

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.f* ***Providing scientific and technical assistance to the Commission within the scope of their mission.***

- *Art. 94.2.h* ***Collaborating within the scope of their mission with laboratories in third countries and with the European Food Safety Authority (EFSA), the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC).***

- ~~*Art. 94.2.i* ***Assisting actively in the diagnosis of outbreaks in Member States of foodborne, zoonotic or animal diseases, or of pests of plants, by carrying out confirmatory diagnosis, characterisation and taxonomic or epizootic studies on pathogen isolates or pest specimens.***~~

- *Art. 94.3.* ***European Union reference laboratories shall publish the list of the national reference laboratories designated by the Member States in accordance with Article 100(1).***

Sub-activity 3.1 *(• Art. 94.2.f / Art. 94.3)*

Objectives:
Technical and scientific assistance to the European Commission

Description:
Support and assistance (e.g. conducting surveys, additional reports, meetings, provision of measurement capacities, etc.) will be provided to the European Commission upon request.

The following activities are fixed for 2018:

- *Discussion of a draft revision of Commission Decision (CD) 2002/657/EC*
At the meeting of the Expert Committee on Residues of Veterinary Medicinal Products in June 2015, the MS indicated that they considered a review of Commission Decision (CD) 2002/657/EC as necessary. Subsequently the EURLs were asked to support DG SANTE in this process. In September 2015 the EURLs carried out a survey among the NRLs on their view on required changes in this Decision. An evaluation of this survey was done and led to a working paper. The finalisation of this paper depends on the decision of COM which legal status the revision of Commission Decision (CD) 2002/657/EC shall have in future.

- *Analysis of national residue monitoring plans of the MS*

- *Collaboration with EFSA, participation in VDR network meetings*

- *Publication of a list of the national reference laboratories designated by the Member States in accordance with Art. 100(1)*

Expected Output:
Report on NRCP evaluation; current NRL-list; working paper on Rev. of CD 2002/657/EC

Duration:
2018 and ongoing

Sub-activity 3.2 *(• Art. 94.2.h)*

Objectives:
Collaboration with European and international organisations (EFSA, EMA, JRC/IRMM, Eurachem, BIPM, CEN, ISO, …) and third countries (international networking and scientific exchange)

Description:
3.2.1
Technical and scientific support will be provided to the Commission institutions DG SANTE, DG JRC (IRMM), EMA and EFSA. The cooperation with international organisations is an ongoing task and will be intensified as far as possible. At the moment the EURL is directly cooperating in the Codex Alimentarius Committees CCRVDF and CCMAS, supporting IAEA activities (training, method data base), as well as in the CCQM working group OAWG of the BIPM. Furthermore, input to ISO working groups for standardisation and CEN working groups for standardisation is given via BVL representatives.

Expected Output:
Internal documents, method evaluations for EMA

3.2.2
The collaboration with official control laboratories in third countries is an important activity in order to strengthen food control in these countries and to achieve standards that offer equivalent guarantees to those applied in the Union.

Hence the same support as for NRLs listed under 1.1, 1.2., 2.1, 2.3 and 2.5 is provided.

Furthermore, experts from third country laboratories are invited to participate in EURL workshops (2.2) and proficiency tests (1.3). Additional assistance (e.g. reference materials, standard substances) is provided upon request.

Long-standing cooperations exist among others with Albania, Serbia, Macedonia, Russia, China, Morocco, Canada and Thailand. The Veterinary Public Health Laboratory (VPHL), Bureau of Quality Control of Livestock Products (BQCLP) and Department of Livestock Development (DLD) in Thailand is the ASEAN Food Reference Laboratory for Veterinary Drug Residues. Hence it is the key contact for the food control laboratories in the ASEAN countries. In 2017 a first common training/workshop for ASEAN countries was organised under participation of the EURL Berlin and shall be repeated from time to time.

Support (analytical methods, SOPs, QA, QC, validation, legislation, specific practical or theoretical training, PT follow-up) is provided upon request. For 2018 no specific activities are planned.

Expected Output:
Scientific exchange; strengthening of official control in third countries; improved safety of food entering the EU; provision of information on analytical methods; scientific support via e-mail or telephone

Duration:
2018 and ongoing

Sub-activity 3.3 *(Art. 94.2g)*

Objectives:
Participation in symposia, workshops and seminars for the dissemination of scientific information and scientific exchange

Description:
In order to fulfil its EURL role as top of the reference laboratory system, the regular participation in scientific conferences, symposia and seminars is mandatory. On the one hand, scientific exchange with experienced researchers and food control experts takes place, on the other hand, the EURL's and COM's views on residue control and its implementation can be presented, discussed and shared. Especially the Symposium on Hormone and Veterinary Drug Residue Analysis, the Euroresidue Conference and the RAFA are important platforms for scientific exchange and networking.

For 2018 the participation in the Symposium on Hormone and Veterinary Drug Residue Analysis is planned.

Expected Output:
Oral presentations; poster presentations; scientific networking

Duration:
2018 and ongoing

Sub-activity 3.4 *(• Art. 94.2.f)*

Objectives:
Ensuring a sound and efficient management of the EURL funding cycle

Description:
To ensure a sound and efficient management of the EURL/EURC funding cycle, several reports are to be issued, e.g. the technical and financial reports on the past EURL working periods as well as the cost estimate and work programme for future periods, performance indicators if applicable, etc.

The following activities are fixed for 2018:
Financial report (2016/2017); technical report (2016/2017)
Draft work programme 2019/2020; estimated budget 2019/2020

Expected Output:
Technical and financial reports; work programme and estimated budget

Duration:
2018 and ongoing

4 REAGENTS AND REFERENCE COLLECTIONS

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.*j ***Coordinating or performing tests for the verification of the quality of reagents and lots of reagents used for the diagnosis of foodborne, zoonotic or animal diseases and pests of plants.***

- *Art. 94.2.k* ***Where relevant for their area of competence, establishing and maintaining:***
  - ***i. reference collections of pests of plants and/or reference strains of pathogenic agents;***
  - ***ii. reference collections of materials intended to come into contact with food used to calibrate analytical equipment and provide samples thereof to national reference laboratories;***
  - ***iii. up-to-date lists of available reference substances and reagents and of manufacturers and suppliers of such substances and reagents.***

Sub-activity 4.1 *(Art. 94.2.k iii)*

Objectives:
Provision of up-to-date lists of available standard substances and matrix reference materials

Description:
Suitable (pure) reference standards and incurred reference materials are the basis of a successful method development, method validation and method performance control.

Via the FIS-VL portal, the EURL provides a current list of standard reference substances and available reference materials (necessary for the control tasks within the responsibility of the EURL Berlin). Reference materials and reference standards which are in stock at the EURL, are provided to the NRLs on request (see 1.2) and are continuously tested for stability.

Expected Output:
Up-to-date lists of available standard substances and matrix reference materials

Duration:
2018 and ongoing

5 REQUIREMENTS RELATED TO OTHER LEGISLATION

Please specify applicable legislation:

Sub-activity 5.1 *(name of Sub-activity)*

Objectives:
Maintaining accreditation according to ISO 17025 and ISO 17043 (PT-provider)

Description:
The QM system according to ISO 17025 is continuously maintained, developed further and has recently been extended to an accreditation as proficiency test provider according to ISO 17043. Costs (including fees for annual visits of the accreditation body) are not explicitly included.

Anyhow the participation in PTs by commercial providers is necessary to document and prove our proficiency outside the framework of our own proficiency tests. This is essential to fulfil the requirements of EA and of the German accreditation body (DAkkS). Furthermore, this way, PT providers can be checked for quality (to give recommendations to NRLs).

Participation depends on the range of PTs offered by commercial providers. So far the programmes for 2018 have been published only in parts, so that we cannot state yet in how many and in which PTs we will participate.

Expected Output:
Certificates by PT providers; successful accreditation body audits

Duration:
2018 and ongoing

Sub-activity 5.2 *(name of Sub-activity)*

Objectives:
Preparation for accreditation according to ISO 17034 (reference material producer)

Description:
Certified reference materials are the key tool for an international comparability of measurement results. The EURL has long-term experience in the preparation of incurred reference materials (i.e. materials produced in animal studies) for proficiency testing, anyhow, so far, not with the aim of providing certified material according to ISO 17034.

Based on the existing competence, the present quality management system shall be adopted aiming at the preparation for an accreditation as reference material provider.

This would be a very useful supplement to the status of the BVL as designated institute for residues of veterinary drugs in food and its ability to provide SI-traceable reference values for these materials (based on its entries in the calibration and measurement data base of the BIPM). The accreditation could not only support the EU-wide comparability of measurement results, but also the world-wide acceptance of measurement results.

Expected Output:
Revised quality management system ready for accreditation

Duration:
2018 / 2019

REMARKS

(if necessary)

EURL-CEFAO

WORK PROGRAMME of EURL for

CHEMICAL ELEMENTS IN FOOD OF ANIMAL ORIGIN

PERIOD: 2018

Version 1.1
(date 18/12/2017)

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SUMMARY

INTRODUCTION

The function and duties of the European Union Reference Laboratories are described in Article 94 of Regulation (EU) 2017/625 of the European Parliament and of the Council of 15 March 2017 (Official Journal of the European Union L 95, 7.4.2017).

As for the European Union Reference for Chemical Elements in Food of Animal Origin (EURL-CEFAO), it is responsible for the residues listed in the Annex I, Group B3(c), of Council Directive 96/23/EC of 29 April 1996.

The EURL-CEFAO work programme is drown up on the basis of the objectives reported in the Commission Work Programme for 2018.

Regulation (EU) 625/2017 Art 94(2):
European Union reference laboratories designated in accordance with Article 93(1) shall be responsible for the following tasks insofar as they are included in the reference laboratories' annual or multiannual work programmes that have been established in conformity with the objectives and priorities of the relevant work programmes adopted by the Commission in accordance with Article 36 of Regulation (EU) No 652/2014:
(taking into account Art 147 of (EU) 625/2017)

1 TO ENSURE AVAILABILITY AND USE OF HIGH QUALITY METHODS AND TO ENSURE HIGH QUALITY PERFORMANCE BY NRLs.

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.a* ***Providing national reference laboratories with details and guidance on the methods of laboratory analysis, testing or diagnosis, including reference methods.***

- *Art. 94.2.b* ***Providing reference materials to national reference laboratories***

- *Art. 94.2.c* ***Coordinating the application by the national reference laboratories and, if necessary, by other official laboratories of the methods referred to in point (a), in particular, by organising regular inter-laboratory comparative testing or proficiency tests and by ensuring appropriate follow-up of such comparative testing or proficiency tests in accordance, where available, with internationally accepted protocols, and informing the Commission and the Member States of the results and follow-up to the inter-laboratory comparative testing or proficiency tests.***

- *Art. 94.2.l* ***Where relevant for their area of competence, cooperate among themselves and with the Commission, as appropriate, to develop methods of analysis, testing or diagnosis of high standards.***

Sub-activity: 1.01 Providing NRLs with details and guidance on analytical methods
(Art. 94.2.a)

Objectives: keep NRLs and official laboratories informed on the available standard methods as well as on the EURL-CEFAO methods in the field of its competence
Description: the list of the standard methods already uploaded on the EURL-CEFAO's website will be regularly updated. According to the request of the DG-SANTE, the EURL-CEFAO analytical methods will be moved from restricted area to public access of the website.
Expected Output: updating of the list of the standard methods, updating and moving of the list of the EURL-CEFAO methods to public area of the website.
Duration: over the year 2018

Sub-activity 1.02 Follow up on request from NRLs for providing analytical standards
(Art. 94.2.b)

Objectives: provide the NRLs with reference materials (extra samples of EURL-CEFAO PTs) to be used for their analytical activity taking under control any reference material stored in the EURL-CEFAO's facilities in order to make the materials promptly available for the NRLs.
Description: according to the EURL-CEFAO policy of optimizing the cost benefit ratio some supernumerary samples are always produced in the occasion of each PT. In general, the EURL-CEFAO is able to prepare a number of PT samples as high as possible using the foreseen funds. For the 2018 PTs some extra samples of frozen mussels and transformed food will be available for the NRLs. Furthermore, leftover materials from previous PTs will make available upon request.
Expected Output: use of the provided materials by NRLs for their internal scopes. Publication of EURL-CEFAO reference materials list on the free area of its web site.
Duration: over the year 2018

Sub-activity 1.03 Organization of Proficiency Test and follow up on results
(Art. 94.2.c)
1.03.1 Organization of PTs

Objectives: organization of Proficiency Tests that allow the network to apply new analytical methods or to verify the performance of those already used
Description: The methods referred to Art. 94.2 a) can be applied for quantifying analytes included in the PTs planned by the EURL-CEFAO in 2018. Therefore, the application of these methods or other suitable ones, including in-house methods, will be coordinated by organizing adequate PTs.
In particular, two inter-laboratory comparative tests will be organized. The first exercise will be based on the determination of As, Cd, Pb, Ni and Hg in frozen mussels, while the second one will be based on the quantification of Cd, Pb, Hg and Sn in transformed food. After each exercise the EURL-CEFAO will perform a follow-up activity and will inform the EC of the outcome, if necessary.
PTs will be organized following international standards as the EURL-CEFAO is an accredited PT provider (ISO 17043:2010).
The organization of extra-exercises for underperforming laboratories will be also considered as an useful and alternative means to assist the NRLs.
Expected Output: organization of two PTs on the determination of analyte/matrix combination included in methods of Art. 94.2 a). Organization of extra exercises for underperforming laboratories, if relevant.

Duration: over the year 2018

1.03.2 Follow up and communication of the PT results

Objectives: verify the steadiness of the performances of each laboratory and as well as the general behaviour of the network, evaluating the control charts of z-scores, checking the performance of the methods used by the NRLs for quantification of analytes not included in the previous EURL-CEFAO's PTs or applied to new matrices. Assisting the NRLs by training them, by visiting one of them or by organizing extra exercises.
Description: NRLs' performances will be monitored by the EURL-CEFAO also verifying the steadiness of their performances by updating the control charts of z-scores. Each NRL can verify its chart in the restricted area of the EURL-CEFAO's website. Follow-up actions will be made by giving the laboratories some suggestions. In particular, NRLs that need a specific analytical support will be contacted and a training will be proposed to them (see 2.03). They can be also visited (see 2.04) or provided with an extra exercise (see 1.03).
Expected Output: carrying out adequate follow-up activities taking especially into account the difficulties encountered by the NRLs in the application of methods referred to Art. 94.2 a) as well as the outcome of the control-carts of z-scores. Organization of training, visit and extra exercises for NRLs.
Duration: over the year 2018

1.03.3 Preparation of incurred samples

Objectives: Studies of new matrix of interest for the network (feasibility study).
Description: Feasibility studies will be carried out to produce a new material for 2019.
Based on the requests of the NRLs and the matrices analysed in the EU NRMPs, egg will be selected as new material. In particular, the freeze-dried procedure as well as the spiking step will be carefully evaluated.
Expected Output: Development of a procedure to produce freeze-dried egg as a new material
Duration: 2 months

Sub-activity: *1.04 Cooperation and meetings with other EURLs*
(Art. 94.2.l)

1.04.1 Meetings with other EURLs

Objectives: Meeting of all the EURLs, meeting with the "residue" EURLs
Description: The Director will attend the annual meeting of all the EURLs organized by the COM.
As for the revision of the Reg. 657/2002 (or other topics of interest), a meeting with the other "residue" EURLs will be attended, when organized.
Expected Output: participation in the "all EURLs" meeting, participation in the "residue" EURL meeting, when organized. Collaborating with the EURLs for revision of the Reg. 657/2002, for establishment of a common web site(1.04.2) and for harmonization of PT protocol (1.04.3) or other topics of interest.
Duration: 2 weeks

1.04.2 Establishment of a common website for the "residue" EURLs

Objectives: establishment of a common website for the "residue" EURLs
Description: the EURL-CEFAO will collaborate with the other three "residue" EURLs for the establishment of a common web site in order to facilitate the exchange of information.
Expected Output: having a common web site where laboratories can find information relating to the "residue" EURLs.
Duration: over the year 2018

1.04.3 Harmonization of proficiency test protocols within the "residue" EURLs

Objectives: proposal of harmonized PT protocols in the residue field
Description: the "residue" EURLs will try to harmonize some aspects of the organisation of their proficiency test protocol considering their different fields of activity and their accreditation status.
Expected Output: drafting a common protocol for the organization of PT covering the aspects of common interest
Duration: over the year 2018

Sub-activity: *1.05 Development and validation of analytical methods*
(Art. 94.2.l)

Objectives: development of new analytical methods, maintenance and improvement of those already in place and maintenance of the accreditation status according to the ISO /IEC 17025.
Description: the accreditation according to ISO 17025 requires a regular updating/reassessment of validation for the accredited methods as well as a continuous check of the methods performance. All the analytical methods included in the scope of accreditation will be regularly monitored through certified reference materials, building of control charts and participation in adequate PTs. The laboratory will undergo a visit from the Accreditation Body on yearly basis as well.
As for the study of new methods, two objectives are pursued in the planning: provide the NRLs with analytical procedures to be applied to the new matrix/analyte combinations included in the EURL-CEFAO PTs, and develop new methods of particular interest for the network or necessary to face emerging topics. In both cases, the results of this activity is shared with the NRLs as these methods are made available on the web site.
The analytical activity will be focused on Tin (Sn), Nickel (Ni) and Selenium (Se). Sn is a chemical element for which a Maximum Level is established in Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. In particular, the content of Sn in canned foods, other than beverages, is considered of particular interest for the network. Therefore, a transformed food will be selected as matrix to be considered for both analytical and PT purposes.
Since from 2017 Ni has been included in the EURL-CEFAO's analytical activity following the Commission Recommendation (EU) 2016/1111 of 6 July 2016 on the monitoring of nickel in food. In particular, Member States are recommended to consider the monitoring of the presence of Ni in bivalve molluscs in their plans. In addition, the intrinsic difficulty of Ni analysis will account for considering the inclusion of its determination in mussels as a focus of the EURL-CEFAO's analytical activity.
Over the years some NRLs asked the EURL-CEFAO for suggestions on the analysis of Se in matrices of interest for the network. Furthermore, EFSA in 2014 drew up an opinion on the dietary reference values for Se pointing the importance of its intake in particular for children. This analyte can be measured using a variety of techniques, but furnace Atomic Absorption Spectrometry (AAS), Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) and Inductively Coupled Plasma

Mass Spectrometry (ICP-MS) are most commonly used. As the level of Se in certain matrices is extremely low, ICP-MS is the preferred technique to be applied. All conventional instruments generate plasma with argon gas, but this poses problem for Se analysis due the formation of a lot of interferences. In fact, at ICP-MS operating temperatures, Ar forms a plethora of interferences by combining itself with the components of the sample (e.g. ArN, ArO and ArCl). Therefore, quantification of Se can be extremely difficult depending on its level of concentration as well as on the matrix analysed. Overcoming the interferences is a key point to develop an adequate analytical method but it can be a very difficult procedure to assess. In fact, there are a lot of methods to eliminate the interferences but they could be not easy to set up and apply. All this considered, the development of a method for determination of Se in matrices, such as meat, by ICP-MS is considered of interest for the network and it will be included in the analytical activity of the EURL-CEFAO.
Expected Output: Development of a method for determination of Sn in transformed food by ICP-OES. Development of a method for quantification of Ni in mussels by ICP-MS. Development of a method for analysis of Se in meat. Dissemination of the new methods (1.01), including their main validation parameters, to the NRLs. Confirmation by the Accreditation Body of all the methods included in the scope of accreditation
Duration: over the year 2018

Sub-activity: *1.06 Analysis of official samples*
(Art. 94.2.b)

Objectives: providing scientific and technical assistance to the Commission, especially in cases where Member States contest the results of analyses;
Description: the EURL-CEFAO, upon request of the COMM or MSs, is available to perform analysis on official samples, once it has established its competence in the field.
Expected Output: performing analysis of official samples to settle controversies among MSs
Duration: over the year 2018

2 TO PROVIDE SCIENTIFIC AND TECHNICAL ASSISTANCE TO NRLs

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.d* ***Coordinating practical arrangements necessary to apply new methods of laboratory analysis, testing or diagnosis, and informing national reference laboratories of advances in this field.***

- *Art. 94.2.e* ***Conducting training courses for staff from national reference laboratories and, if needed, from other official laboratories, as well as of experts from third countries.***

- *Art. 94.2.g* ***Providing information on relevant national, Union and international research activities to national reference laboratories.***

Sub-activity: 2.01 *Providing technical and scientific support to NRLs*
(Art. 94.2.d)

Objectives: giving theoretical and practical assistance to the NRLs according to the EURL-CEFAO's tasks. Drawing up specific guidelines for the application of methods proposed by the EURL-CEFAO within its PTs. Informing the NRLs of changes in legislation and advances in the field of chemical elements' analysis by updating the specific section of the website, "Legislation and Working Documents".
Description: the EURL-CEFAO's website will be updated on yearly basis to disseminate information about any novelty in analytical methods of interest for the network, scientific publications and relevant EU legislation (see 1.01 and 2.05). New methods, developed by the EURL-CEFAO within its PTs, will be distributed to the NRLs as guidelines to provide the laboratories, which do not have suitable methods in place, with methods useful for participating to the EURL-CEFAO's PTs (see 1.05). Based on the expertise of the staff any demands from NRLs, and falling within the competence of the EURL-CEFAO, will be promptly answered.
Expected Output: prompt and fruitful assistance to the NRLs in respect with the application of new analytical methods in their field of competence especially for methods developed by the EURL-CEFAO that can be used in the EURL-CEFAO's PTs. Prompt assistance to the NRLs for whatever topics falling within the expertise and tasks of the EURL's staff in particular in respect with emerging issues.
Duration: over the year 2018

Sub-activity: 2.02 *Organization of workshops*
(Art. 94.2.e)

Objectives: inclusion of issues regarding research activities into the agenda of the annual workshop. In particular, topics proposed by the speakers must fall within the field of interest for the network. Creation of occasions to exchange ideas and points of view among participants increasing the relationship among the laboratories belonging to the network.
Description: An "Annual NRLs–EURL Workshop" will be organised in order to propose and discuss specific topics of common interest. Researchers from NRLs or from international institution will be invited to present their official activities as well as results of their researches. A poster session will be also organized to share as many information as possible.
Representatives of laboratories of third countries, who are in touch with the EURL-CEFAO, will be also invited to attend the workshop in order to promote the collaboration and the exchange of opinions on scientific issues.
Expected Output: presentation of research activities and topics relevant to the legislation in force through speeches or poster during the annual workshop.
Duration: 5 months

Sub-activity: 2.03 *Organization of training courses*
(Art. 94.2.e)

Objectives: organization of training courses for the benefit of the representatives of NRLs. The trainings can be organized in the NRLs or EURL-CEFAO facilities to meet the needs of the NRLs. Also trainings for experts of third countries will be organised upon request.
Description: the EURL-CEFAO is available to train NRLs upon request for specific issue of its competence as well as Official Laboratories of candidate EU Member States and Third Countries. In case of continuous underperformances or underperformances difficult to overcome, NRLs will be contacted and a training will be proposed to them.
Expected Output: organization of at least one training per year for representatives of NRLs or experts from third countries. Good feedback from the participants (satisfactory responses to the questionnaires).
Duration: 2 weeks

Sub-activity: 2.04 *Visits of NRLs*
(Art. 94.2.d and e)

Objectives: Assisting the NRLs by visiting their laboratories
Description: Follow-up actions will be made by giving the laboratories some suggestions or advises as well as by planning a visit at the NRLs' laboratories (1.03.2). In particular, NRLs that need a specific analytical support will be contacted and a training will be proposed to them (2.03). Laboratories to be visited will be selected on the basis of the following criteria: underperforming laboratories, new laboratories entered the network or underperforming laboratories that have changed their analytical technique, laboratories already visited that still evidence the need of an extra dedicated training.
Expected Output: carrying out a visit at the facilities of one NRL belonging to the EURL-CEFAO's network
Duration: 1 week

Sub-activity: 2.05 Providing relevant information on research activities to NRLs
(Art. 94.2.g)

Objectives: Informing the NRLs of advances in the field of chemical elements' analysis by updating specific sections of the website (survey of scientific literature) and changes/amendments in the legislation
Description: the EURL-CEFAO's website will be updated on yearly basis to disseminate information about any novelty in analytical methods of interest for the network Research activities available in scientific journals and relevant for the network will be evaluated by the EURL-CEFAO experts and selected to be included in the list of the updated survey of scientific literature (website updating).
Any change/amendment in the legislation of interest will be communicated to the network and the website section regarding the relevant legislation promptly updated.
Expected Output: updating of the EURL-CEFAO website section "Legislation and working documents"
Duration: over the year 2018

Sub-activity: 2.06 *Updating and publication of the list of NRLs*
(Art. 94.2.g)

Objectives: keep the network updated regarding the laboratories appointed as NRLs
Description: the list of the appointed NRLs is present in the free area of the EURL-CEFAO website. The EURL-CEFAO will promptly update the document in case of changes/news communicated by the COM.
Expected Output: publishing an updated list of the NRLs belonging to the EURL-CEFAO's network.
Duration: over the year 2018

3 TO PROVIDE SCIENTIFIC AND TECHNICAL ASSISTANCE TO THE EUROPEAN COMMISSION AND OTHER ORGANISATIONS

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.f* ***Providing scientific and technical assistance to the Commission within the scope of their mission.***

- *Art. 94.2.h* ***Collaborating within the scope of their mission with laboratories in third countries and with the European Food Safety Authority (EFSA), the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC).***

- *Art. 94.2.i* ***Assisting actively in the diagnosis of outbreaks in Member States of foodborne, zoonotic or animal diseases, or of pests of plants, by carrying out confirmatory diagnosis, characterisation and taxonomic or epizootic studies on pathogen isolates or pest specimens.***

Sub-activity: 3.01 *Technical and scientific assistance to the COM*
(Art. 94.2.f)

3.01.1 Analysis of NRMPs of the MSs

Objectives: performing the evaluation of the National Residues Monitoring Plans (NRMPs) according to the expertise of the EURL-CEFAO staff and meeting the criteria indicate by the EC.
Description: The NRMPs will be evaluated taking into account the criteria indicated by the EC. Specific observations will be made, if appropriate.
Expected Output: Issuing of a Report on the evaluation of NRMPs and submission to the EC in due date.
Duration: 1 month

3.01.2 Conducting surveys at the request of COM

Objectives: providing expertise and technical and scientific support to the European Commission (EC) upon request
Description: The EURL-CEFAO is available to conduct surveys, according to its field of activity, at the request of the EC also involving the NRLs network. This task will be accomplished by the members of the EURL staff more competent in the specific issue.
Expected Output: providing surveys to COM as prompt as possible, upon request.
Duration: over the year 2018

3.01.3 Professional expertise and technical and scientific support upon request

Objectives: response to any questions from the COM falling within the mission of the EURL-CEFAO
Description: requests from the COM for scientific and technical assistance in the field of competence of the EURL-CEFAO will be treated as a priority and all staff will be involved according to their expertise.
Expected Output: prompt replying to any questions from the COM falling within the mission of the EURL-CEFAO
Duration: over the year 2018

Sub-activity: 3.02 *Collaboration with European and international organization and third countries (Art. 94.2.h)*

Objectives: collaboration with Eurachem, CEN and LANAGROS (Ministerio da Agricultura, Pecuaria e Abastecimento-Brazil) and any other relevant request of collaboration.
Description: The EURL-CEFAO's staff is already involved in the activity of CEN/TC 275/WG 10 (elements and their chemical species). This activity will continue by participating in the meetings of the working group as well as by giving a contribution to the topics under discussion. The involvement in the Eurachem working groups (Eurachem Working Group on Proficiency Testing and EEE Proficiency Testing Working Group - "Proficiency Testing in Accreditation") will be strengthened by contributing to documents and attending the meetings. The collaboration with LANAGRO/RS will be continued as well. Any request of collaboration from national/EU/third countries institution will be evaluated and, if relevant, accepted.
Expected Output: participation to the activities of the working groups in which the EURL-CEFAO's experts are involved. Presentation of at least one lecture or poster in the selected international congress. Availability to continue the collaboration with LANAGROS laboratory and with other institutions.
Duration: over the year 2018

Sub-activity: 3.03 *Participation in workshops and seminars for the dissemination of scientific information*
(Art. 94.2.h)

Objectives: participating in international congresses to spread information on the EURL-CEFAO's activity and to improve its knowledge of topics of interest
Description: As for participation in international congresses, the scientific conferences to attend either as speaker or as participant, will be carefully selected among those on topics related to the EURL-CEFAO activity
Expected Output: Presentation of at least one lecture or poster in the selected international congress.
Duration: 2 months

Sub-activity: 3.04 *To ensure a sound and efficient management of the EURL funding cicle (Art. 94.2.f)*

3.04.1 EURL work programme

Objectives: preparing a work programme to be approved by the EC
Description: the EURL-CEFAO prepares a suitable WP complying with all its tasks and paying attention to activity of interest for the NRLs. In doing this, emerging problems and issues proposed by the NRLs .will be also considered. As for the budget request it will be strictly proportioned to the planned activities
Expected Output: planning activities to monitor and/or improve the performance of the network, to propose new issues and to face changes in the legislations and emerging problems.
Duration: 1 week

3.04.2 EURL reports

Objectives: issuing all the reports requested by the EC and those relevant to the activities performed (e.g. PT reports)
Description: the EURL-CEFAO is requested to maintain the EC updated on its activities, for this reason reports will be produced for any key activity (e.g. Report of the Workshop, Report of visit to NRLs, etc) As for the activity as accredited PT Provider the EURL has specific procedures in which are specified the reports that have to be provided to participants.
Expected Output: issuing all reports requested by the EC and by the Quality Management system in due time
Duration: over the year 2018

4 REAGENTS AND REFERENCE COLLECTIONS

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.*j ***Coordinating or performing tests for the verification of the quality of reagents and lots of reagents used for the diagnosis of foodborne, zoonotic or animal diseases and pests of plants.***

- *Art. 94.2.k* ***Where relevant for their area of competence, establishing and maintaining:***
  - ***i. reference collections of pests of plants and/or reference strains of pathogenic agents;***
  - ***ii. reference collections of materials intended to come into contact with food used to calibrate analytical equipment and provide samples thereof to national reference laboratories;***
  - ***iii. up-to-date lists of available reference substances and reagents and of manufacturers and suppliers of such substances and reagents.***

Sub-activity 4.01 Up-to-date lists of reference substances/reagents and of manufacturers and suppliers *(Art. 94.2.k)*

Objectives: provide the users of the EURL-CEFAO website with a list of reference materials in food matrices (animal origin) or reagents for special uses
Description: reference materials with certified mass fractions (CRMs) for chemical elements in food of animal origin are not always easy to find. A list, as exhaustive as possible, of CRMs will be published on the public area of the EURL-CEFAO web site. The list will include the certificate for each CRM, the indication of the manufacturers and the link to their web site.
Moreover, a list of reagents for special uses (e.g. isotopic dilution or speciation of chemical elements) will be likewise made available. The indication of the relevant suppliers will be also provided.
Expected Output: publication of the lists of CRM and reagent for special uses, periodic check and updating of these lists.
Duration: over the year

5 REQUIREMENTS RELATED TO OTHER LEGISLATION

Please specify applicable legislation: Not relevant
(Number of Sub-activity boxes can be adjusted)

REMARKS

1. As for the duration of the activities we have indicated the period in which it takes place, in most of the cases the whole year.
2. As for consumables the costs of the accreditation (ISO 17025 and ISO 17043) have been included in the ISS co-financing.
3. As for the workshop, we have considered the possibility to invite more than one person from different NRLs of the same MSs as well as representative of NRLs from third countries (total of 35 participants)
4. As for the training, it has been foreseen for two people coming from the same NRL

WORK PROGRAMME of EURL for Growthpromoting agents, sedatives and mycotoxines in food of animal origin

PERIOD: 2018

Version 2.0
(date 18/12/2017

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SUMMARY

INTRODUCTION

Legal functions and duties
The functions and duties of the EU Reference Laboratory are described in Article 94 of Regulation (EC) No 2017/625 of the European Parliament and of the Council of 7 April 2017 (Official Journal of the European Union L 95/I, 7.04.2017, pp 1-141).

The general objective of the Commission for the period 2018-2020 is "to contribute to a high level of protection for consumers and the environment while favouring competiveness and the creation of jobs[1]". This general objective is elaborated in four operation objectives which are the foundation of the EURL workprogramme for 2018.

The EURL workprogramme is divided in 4 parts, linked to the five operation objectives (last objective not applicable). For each operational objective individual tasks have been formulated which are described in more detail for the one year period.

Structure Workprogramme EURL for residues based on OCR 2017\625 article 94

1. To ensure availability and use of high quality methods and to ensure high quality performance by NRLs.

1.1 Provide NRLs with details and guidance on the methods of laboratory analysis, testing or diagnosis, including reference methods. (a)

1.1.1 Updating the EU RL website

1.2 Follow up on requests from NRLs for providing analytical standards (b)

1.3 Organisation of proficiency tests and follow up on the results (c)'

1.3.1 Organisation of PTs

1.3.2 Follow up on and communication of the PT results

1.3.3 Preparation of incurred samples

1.4 Cooperation and meetings with other EURLs (l)

1.5 Development and validation of analytical methods (l)

1.6 Analysis of official samples (b)

2. To provide scientific and technical assistance to NRLs

2.1 Providing technical and scientific support to NRLs (d)
2.2 Organisation of workshops (e)
2.3 Organisation of training courses (e)

[1] Commission implementing decision of 24.7.2015 on the adoption of the work programme of the Commission for the years 2015 and 2016 and on the financing of the Union contribution to the European Union Reference Laboratories

2.4 Visits of NRLs (d and e)
2.5 Providing relevant information on national, Union and international research activities to NRLs (g)
2.6 Updating and publication of the list of NRLs

3. To ensure scientific and technical assistance to the European Commission and other organisations

3.1 Technical and scientific assistance to the Commission (f)

e.g. 3.1.1 Analysis of National residue monitoring plans of the MS (f)

e.g. 3.1.2 Conducting surveys at the request of COM(f)

3.2 Collaboration with European and international organisations (EFSA, EMA, Eurachem, CEN, ISO, …) and Third Countries (h)

3.3 Participation in symposiums, workshops and seminars for the dissemination of scientific information. (h)

3.4 To ensure a sound and efficient management of the EURL/EURC funding cycle.

3.4.1 EURL work programmes

3.4.2.EURL reports

3.4.3 EURL performance indicators

4. Reagents and reference collections

4.1 Up to date lists of available reference substances and reagents and of manufacturers and suppliers of such substances and reagents (k)

Regulation (EU) 625/2017 Art 94(2):
European Union reference laboratories designated in accordance with Article 93(1) shall be responsible for the following tasks insofar as they are included in the reference laboratories' annual or multiannual work programmes that have been established in conformity with the objectives and priorities of the relevant work programmes adopted by the Commission in accordance with Article 36 of Regulation (EU) No 652/2014:
(taking into account Art 147 of (EU) 625/2017)

1 TO ENSURE AVAILABILITY AND USE OF HIGH QUALITY METHODS AND TO ENSURE HIGH QUALITY PERFORMANCE BY NRLs.

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.a* ***Providing national reference laboratories with details and guidance on the methods of laboratory analysis, testing or diagnosis, including reference methods.***
- *Art. 94.2.b* ***Providing reference materials to national reference laboratories***
- *Art. 94.2.c* ***Coordinating the application by the national reference laboratories and, if necessary, by other official laboratories of the methods referred to in point (a), in particular, by organising regular inter-laboratory comparative testing or proficiency tests and by ensuring appropriate follow-up of such comparative testing or proficiency tests in accordance, where available, with internationally accepted protocols, and informing the Commission and the Member States of the results and follow-up to the inter-laboratory comparative testing or proficiency tests.***
- *Art. 94.2.l* ***Where relevant for their area of competence, cooperate among themselves and with the Commission, as appropriate, to develop methods of analysis, testing or diagnosis of high standards.***

Introduction

Development and validation of state of the art analytical methods is one of the major tasks of the EURL. New analytes, or metabolites of compounds, will have to be included on a regular basis in analytical methods and new technologies will have to be implemented. Based on the results of research activities within the EURL-NRL network, methods will have to be re-evaluated on specific aspects. Adequately validated methods for all analyte-matrix combinations included in the list of Recommended Concentrations for Control (CRL Guidance paper 2007), or for new MRPLs or the RPA-values to be set will be maintained and made available on request. The EFSA document with regard to

toxicological limits on veterinary medicinal products in food of animal origin will also be included in setting priorities. Priorities are set on the basis of input by the Commission, discussions with the NRLs, e.g. during annual workshops and the EURLs view on important scientific and technical trends and innovations.

New methods will be developed for new classes of compounds, not yet included in the CRL-guidance paper, or for analytes for which methods have proven to be inadequate. Developing and implementing efficient strategies for the control on natural hormones will remain an important research topic during the coming years. This includes four different classes of compounds: the classic natural hormones, the so-called minor androgens that can be present or formed in biological samples, protein hormones and substances that can be foodborne or stress related (e.g. corticosteroids). This part of the work programme is partly based on the EURL Reflection paper from 2014. This Reflection paper will be updated in 2018.

1. To ensure availability and use of high quality methods and to ensure high quality performance by NRLs.

1.1 Provide NRLs with details and guidance on the methods of laboratory analysis, testing or diagnosis, including reference methods. (a)

1.1.1 Updating the EU RL website

The EURL website currently contains standard operating procedures for analyte matrix combinations in the field of the growthpromoter EURL. The website will be updated with new analytical methods and new extended- and validated method in 2018. Publication of validations, analytical methods and research reports on the public EURL website.

1.2 Follow up on requests from NRLs for providing analytical standards (b)

1.2.1 *Collection of standard substances and deuterated internal standards*

Objectives: Provision of standard substances including storage, administration, documentation and shipment.
Description: Acquiring essential standards and internal standards and metabolites. When necessary and possible, selected compounds will be purchased or (custom) synthesised.
Expected Output: Ampoulated reference standards available through EURL webshop

Duration: ongoing whole year

1.3 Organisation of proficiency tests and follow up on the results (c)'

1.3.1 Organisation of PTs

Objectives: Organisation of PT for routinely used method and organisation of research study for new analyte or new analyte-matrix combinations
Description:

a. Continuation A3 in urine PT started November 2017
b. PT Gestagens in kidney fat
c. Research study steroids in meat

Expected Output:

Ringtest reports
Duration: one year

1.3.2 Follow up on and communication of the PT results
Objective: The follow up protocol of the EU DG Santé for proficiency testing needs to be implemented. The 4 EURLs for residues will prepare a harmonised protocol for assessing PT performance of NRLs.

1.3.3 Preparation of incurred samples
Objectives: To produce incurred sample materials for PT and research studies
Description: Perform animal experiment and collect sample materials to be used
Expected Output: Incurred materials for use in PTs and research studies
Materials as Quality Control sets for webshop
Duration: one year

1.4 Cooperation and meetings with other EURLs (l)

Objective: To attend meeting with other EURL. Either organised by DG Santé or organised by 4 EURLs for residues. To coordinate, harmonize the work of the EURL and to work on revision of legislation and guidance documents.

1.4.1 Establishing a webportal for the 4 EURLs for residues. And filling this with the appropriate information.

1.4.2 Harmonisation of proficiency test protocols for assessing PT performance of NRLs: a common protocol for the residues EURLs.

1.5 Development and validation of analytical methods (l)

1.5.1 *Method development*
Objectives: To develop methods for new emerging risk compounds and or methods for known compounds in different matrices or species.
Description:

a. For a number of naturally occurring compounds there is still no possibility to distinguish between exogenous or endogenous origin, eg. zeranol, prednisolone, thiouracil and BST. These compounds are difficult to analyse using gas chromatography coupled to IRMS, the approach used for testosterone and oestradiol. Liquid chromatography is the separation technique of choice for these compounds. Coupling LC to IRMS could be the solution to this problem. In 2018 an interface for coupling LC to IRMS will be bought. Method development for thiouracil and other synthetic natural growth promoters in urine will be started.

b. In 2017 research into the use of new state of the art full scan high resolution GC-mass spectrometry for multi analyte steroid detection and untargeted analysis was started. The preliminary studies into the feasibility of this technique for steroid analysis showed good results. In 2018 the high resolution method for the detection of steroids in urine will be extended. Libraries will be build and a workflow for untargeted analysis will be developed. Method aims at detecting forbidden substances at low levels. Quantification of the compounds will also be possible.

c. Sampling on farm is difficult. Although for a number of compounds this is the best time to test animals. Inspectors have to wait for animals to produce urine and for blood sampling veterinarians are needed. Sampling of bloodspots is easy to perform, quick and can also be done by inspectors. Bloodspot cards can be archived and stored easily and do not take up much space. In 2018 the proof of principle for the steroidesters in blood will be developed and validated. .

d. For several years growth hormone and peptides are being used to increase muscle mass in humans. Farmers "learn" from athletes and these compounds can potentially be misused in animal husbandry. Some peptides have anabolic properties (GHRP's) others inhibit the growth inhibition (myostatine inhibition).

   On the black market there are peptides available who claim to inhibit growth inhibition. At the moment there are no methods available to detect these peptides. On the basis of literature research into the mechanism of these peptides in 2018 a start will be made to develop methods and strategies to detect misuse of these peptides.

Expected Output:
- start with LC-IRMS analysis
- Library for HRMS analysis of steroids with GC-HR-MS. Workflow for untargeted analysis of steroid with GC-HR-MS
- Dry Bloodspot analysis for steroidesters. SOP and validation file.
- Start with method of analysis for peptide growth promoters

Duration: 1 year

1.5.2 *Maintenance or extension of existing analytical methods*

Objectives: Analytical methods need re-validation or extension with new compounds when MRPL or RPA change or in view of the EFSA guideline or in view of more quantitative data collection for EFSA. In 2018 the methods below will be either (re)validated or extended.

Description:

a. In 2017 a profiling analytical method for screening of thiouracil in bovine urine was developed. Thiouracil is a compound which can be formed in the intestine of the bovine and porcine animal. To distinguish thiouracil abuse from endogenously formed thiouracil a biomarker discovery approach was used. A statistical models was developed to discover specific biomarkers for the discrimination. The structure was partly elucidated for a marker for Thiouracil. The marker for rapeseed consumption needs to be elucidated. Development of a new control method for thyrostats based on these new biomarker(s) in urine of porcine animals will be undertaken. The method uses LC-MS/MS.
   Validation of the new method for thiouracil discrimination in porcine urine.
b. Validation of extended method for different forms of IGF-1 using LC-MS/MS. The method will be quantitative for the endogenous forms.
c. LC-MS/MS methods to detect rbST are using antibodies to extract and isolate rbST from biological samples. Since the supply of antibodies is considered as critical, the EURL will produce and make available the antibodies via the webshop for all member states.

Expected Output:
SOP for thiouracil discrimination and validation file
Start extension IRMS for formestane
Validation file different forms of IGF-1 in serum
Availability of antibodies for screening rBST in webshop

Duration: one year

Choose a building block.

1.6 Analysis of official samples (b)
Objectives: Help NRLs with confirmatory analysis on an individual sample basis. Perform arbitration analysis.
Description: Analyse samples from NRLs for confirmation when there are technical problems in NRL or when there is a dispute for arbitration.

Expected Output:
Analysis reports
Duration: depending on requests

2 TO PROVIDE SCIENTIFIC AND TECHNICAL ASSISTANCE TO NRLs

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.d* ***Coordinating practical arrangements necessary to apply new methods of laboratory analysis, testing or diagnosis, and informing national reference laboratories of advances in this field.***
-
- *Art. 94.2.e* ***Conducting training courses for staff from national reference laboratories and, if needed, from other official laboratories, as well as of experts from third countries.***
-
- *Art. 94.2.g* ***Providing information on relevant national, Union and international research activities to national reference laboratories.***

2.1 Providing technical and scientific support to NRLs (d)

2.1.1 *Studies to detect abuse of (semi)- natural hormones*

Objectives: Based on the EURL Reflection Paper (2014), priorities for research are set together with the NRLs.
Description: An update of the reflection paper on the occurrence of natural hormones is foreseen for 2018. New subjects will be picked up in EURL workplan 2019.
Expected output: Update Reflection Paper report
Duration:1 year

2.1.2 Identification of new compounds

Objectives: Identification of new growthpromoting compounds

Description: When preparations are found or new information is gathered on new compounds being misused the identity of such compounds can be elucidated within this activity.
Expected Output: identification of new compounds, illegally used as growth promotors and the availability of a paper on this subject, which is published on the EURL website and which is communicated to the NRLs.
Duration: 1 year

2.1.3 Analytical support
Objective: to help the NRLs and OFL with technical problems on the analysis.

2.1.4 Documentation and information services
Objectives: Developments with respect to analytical methodology, (EU) legislation and the results of relevant scientific studies are constantly monitored. In addition, information on the use of new compounds or alternative approaches to improve the growth of livestock will be collected and used as input for future studies. Communication about issues of interest for NRLs will be through the annual workshop and the EU-RL website.
Description: The EU-RL-website is maintained. The EU-RL website will be maintained with continued efforts to further implement its use within the EU-NRL/OFL network.
The database with EURL literature inclusive scientific reports, will be maintained as a source of information for EURLs and NRLs .
Extension and promoting use of EU-RL web forum for information exchange.
Expected Output: Available information on website
Duration: ongoing whole year

2.2 Organisation of workshops (e)

Objectives: Organisation of an annual workshop to inform NRLs on new methods, new legislation ao and discuss work programmes and PTs. To have information exchange between the NRLs.
Description: Memberstates and a selected number of third countries come to RIKILT for information exchange and discussion on new topics in the growthpromoter field
Expected Output:
Information exchange
Workshop report
Duration: 2-3 days

2.3 Organisation of training courses (e)

2.3.1 Individual based training

Objective: Two or three short visits from NRL scientists to EURL RIKILT to be trained in an analytical method.

2.3.2 Organisation of an additional group training for NRLs or OFLs on analysis of growthpromoters. This training will be organised if a minimum of 5 participants is interested and if subjects are available for which the NRLs want to receive more in depth training.

2.4 Visits of NRLs (d and e)
Objective: Missions to NRLs, visit to NRLs in member states, 2 per year. Missions will be undertaken to specific NRLs on the basis of their individual needs, e.g. in order to discuss and evaluate the

results of a proficiency test, or analytical support. The choice for 2018 will be based on the current progress in the NRLs in the newer EU-Member States. For 2018 Cyprus and Belgium will be visited.
Expected Output:
- visit reports

2.5 Providing relevant information on national, Union and international research activities to NRLs (g)

2.6 Updating and publication of the list of NRLs
Objective: To have an updated list of NRLs in the competence field of our EURL. This list will be published on the website. Changes in institutes, contact names etc. will be updated when received by EURL. Annually during the workshop the NRL are requested to check and if necessary update the information.

Choose a building block.

3 TO PROVIDE SCIENTIFIC AND TECHNICAL ASSISTANCE TO THE EUROPEAN COMMISSION AND OTHER ORGANISATIONS

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.f* ***Providing scientific and technical assistance to the Commission within the scope of their mission.***

- *Art. 94.2.h* ***Collaborating within the scope of their mission with laboratories in third countries and with the European Food Safety Authority (EFSA), the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC).***

- *Art. 94.2.i* ***Assisting actively in the diagnosis of outbreaks in Member States of foodborne, zoonotic or animal diseases, or of pests of plants, by carrying out confirmatory diagnosis, characterisation and taxonomic or epizootic studies on pathogen isolates or pest specimens.***

3.1 Technical and scientific assistance to the Commission (f)

3.1.1 The process of revising Commission Decision 2002\657 has started in 2016. Under the 2016-2017 work program a first draft revised version of CD. 2002/657/EC was prepared. In 2018 assistance will be provided to the

Commission for further amending the document in line with the MSs and the Commissions' comments. If needed the NRLs will be requested to provide input.

3.1.2 Analysis of National residue monitoring plans of the MS (f)

Evaluation of the annual national control plans for the member states.

3.1.3 Upon request of the Commission support through information on analytical methods or through surveys among NRLs.

3.2 Collaboration with European and international organisations (EFSA, EMA, Eurachem, CEN, ISO, …) and Third Countries (h)

EC/EURL related co-operation with International Bodies (e.g. AOAC international, Eurachem, Codex, CVMP, TAIEX, EMA, EFSA, JRCs, IRMM, FVO and IAEA) on method validation, analytical methodology, reference materials and performance quality criteria (communication, co-ordination, and harmonisation).

Example given:

When requested, assist FVO as laboratory expert in audits for third countries.

Cooperate in IAEA coordinate research projects as advisor to third countries

Assist EMA with evaluation of analytical methods in registration files.

3.3 Participation in symposiums, workshops and seminars for the dissemination of scientific information. (h)
Participation in Scientific Committee of VDRA congress.
Presenting oral and poster on scientific research performed within the EURL.

3.4 To ensure a sound and efficient management of the EURL/EURC funding cycle.

3.4.1 EURL work programmes
Compilation of an annual workprogramme and budget forecast

3.4.2.EURL reports
Compilation of an annual report and cost statement

4 REAGENTS AND REFERENCE COLLECTIONS

Please, provided activities related to Regulation (EU) 2017/625:
(Number of Sub-activity boxes can be adjusted by EURL)

- *Art. 94.2.*j ***Coordinating or performing tests for the verification of the quality of reagents and lots of reagents used for the diagnosis of foodborne, zoonotic or animal diseases and pests of plants.***

- *Art. 94.2.k* ***Where relevant for their area of competence, establishing and maintaining:***
  - ***i. reference collections of pests of plants and/or reference strains of pathogenic agents;***
  - ***ii. reference collections of materials intended to come into contact with food used to calibrate analytical equipment and provide samples thereof to national reference laboratories;***
  - ***iii. up-to-date lists of available reference substances and reagents and of manufacturers and suppliers of such substances and reagents.***

4.1 Up to date lists of available reference substances and reagents and of manufacturers and suppliers of such substances and reagents (k)

Objective: To provide the NRLs with information on available standards and providers

5 REQUIREMENTS RELATED TO OTHER LEGISLATION

Please specify applicable legislation:
(Number of Sub-activity boxes can be adjusted)

Not applicable

REMARKS