Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

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

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Progress in Support for the NRL Network

Guidance Updates and Data Bases

Networking, Contact and Information Exchange….

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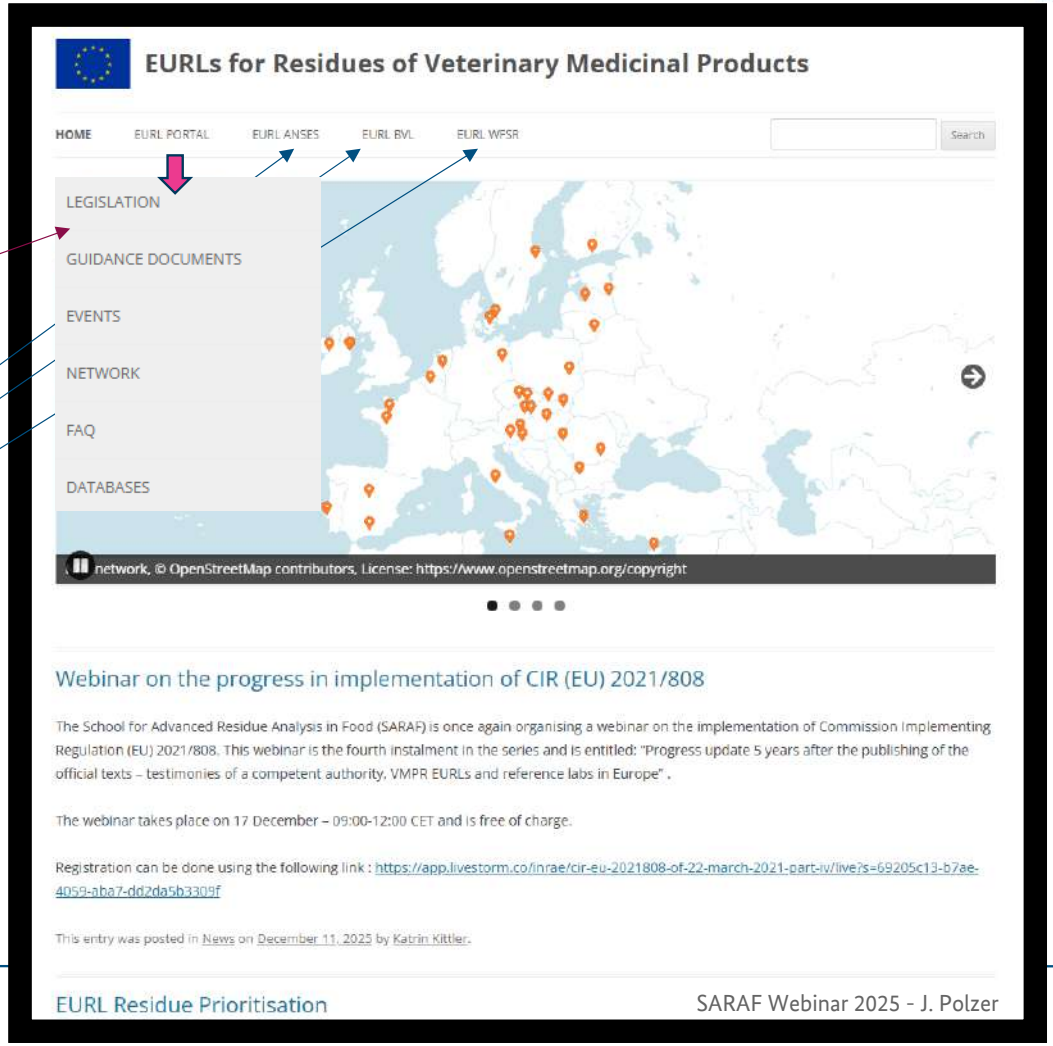
https://eurl-residues.eu/

Legislation and Guidance

Access to individual information / websites of the three VMPR EURLs

Current information



CIR (EU) 2021/808 (consol. 17 February 2025)

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COMMISSION IMPLEMENTING REGULATION (EU) 2021/808

of 22 March 2021

on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC

Qualitative confirmatory analysis	HRMS guidance	MMPR guidance	Substance data base and stability data base
2.1. Performance characteristics to be determined for analytical methods	1.2.4. Specific performance criteria for mass spectrometry 1.2.4.1. Mass spectrometric detection	1.2.1. General requirements for confirmatory methods	2.5. Stability 2.5.1. / 2.5.2 Determination of the stability of the analyte in solution / in matrix

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Table 5

Classification of analytical methods by the performance characteristics that have to be determined

Method	Confirmation		Screening		
	Qualitative	Quantitative	Qualitative	Semi-quantitative (+)	Quantitative
Substances	A	A, B	A, B	A, B	A, B
Identification in accordance with 1.2.	x	x			
CCα	x	x			
CCβ	—		x	x	x
Trueness		x			x
Precision		x		(x)	x
Relative matrix effect/absolute recovery (*)		x			x
Selectivity/Specificity		x	x	x	x
Stability (#)		x	x	x	x
Ruggedness		x	x	x	x

Qualitative confirmatory analysis

The idea : to express that qualitative detection of a banned substance is sufficient for objection.

However, there was and is currently no analytical procedure for a simple yes/no decision for confirmation

https://commons.wikimedia.org/

Requirement for confirmation of A-substances : **use of MS-based techniques**

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Qualitative (semi-quantitative) confirmatory analysis

CHAPTER 2

VALIDATION

2.1. **Performance characteristics to be determined for analytical methods**

By means of the validation of the method, it shall be demonstrated that the analytical method complies with the criteria applicable for the relevant performance characteristics. Different control purposes require different categories of methods. Table 5 determines which performance characteristic shall be verified for which type of method, further explanation of each parameter is given in this chapter.

EURL interpretation:

The usual approach should be to validate confirmatory methods as quantitative methods. If the quantification criteria for A substances are not met, these methods can be used as **"semi-quantitative"** methods.

The CCα shall be determined for confirmatory methods. The CCα shall be established under conditions complying with the requirements for identification plus (semi-)quantification

Calculation methods according to "2.6 Decision limit for confirmation (CCα)"
1 (a) and 1 (c) can be applied (precision requirements in Table 2 of Annex I has not to be met).

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HRMS guidance

For confirmation of the identity of an analyte in high-resolution mass spectrometry (HRMS) the mass deviation of all diagnostic ions shall be below 5 ppm (or in case of m/z < 200 below 1 mDa). On basis of this the effective resolution should be selected fit for purpose and the resolution shall typically be greater than 10 000 for the entire mass range at 10 % valley or 20 000 at full width at half maximum (FWHM).

For HRMS :
definition of mass accuracy and resolution

General :
For identification: identification point system
(4 / 5 identification points for confirmation)

Requirements for precursor ion selection,
product/fragment ion selection, relative ion intensities

Table 3

Identification points per technique

Technique	Identification Points
Separation (mode GC, LC, SFC, CE)	1
LR-MS ion	1
Precursor ion selection at <±0,5 Da mass range	1 (indirect)
LR-MS^n product ion	1,5
HR-MS ion	1,5
HR-MS^n product ion	2,5

HRMS guidance

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- Complexity of new HRMS techniques is **not addressed in CIR (EU) 2021/808**
  - Need of interpretation of the requirements of CIR (EU) 2021/808

EURL / NRL Working Group

e.g. additional definitions ....

- ✓ Collision Cross Section (CCS)
- ✓ Data-independent acquisition (DIA)
- ✓ Dynamic Range
- ✓ Exclusion list
- ✓ Fingerprinting
- ✓ Full Scan MS
- ✓ Full Scan confirmatory analysis
- ✓ High-Resolution Mass Spectrometry (HRMS)
- ✓ Inclusion List
- ✓ Mass extraction window (MEW)
- ✓ Non-target detection
- ✓ Non-target screening
- ✓ Orbitrap
- ✓ Parallel reaction monitoring (PRM)
- ✓ Scan speed
- ✓ Suspect screening
- ✓ Semi-Targeted Analysis
- ✓ Target
- ✓ Target screening
- ✓ Target Sim (t-SIM)
- ✓ Targeted detection
- ✓ Chemical space
- ✓ Componentization
- ✓ Exclusion List
- ✓ Feature extraction
- ✓ Ion mobility
- ✓ MS Ion
- ✓ Quadrupole Orbitrap

HRMS guidance

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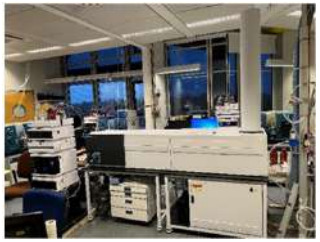
Measurement modes…

Identification critieria fullfilled ?



Measurement Modes	Orbitrap	QToF	Screening / Confirmation	Precursor selection	Fragments (traceable to a	Isotopic pattern/Spectr	Spectra	Ion ratio	Identification point CIR (EU) 2021/808	Relative intensities (ion ratio)	Confirmation by considering
1. Full MS (no fragmentation)	Full scan MS	MS Only (Full MS, Full scan)	x (suspect, non-target) screening only	Accurate mass ≤ 5 ppm	no	yes	Libraries/Databases	Available by comparison with libraries/database. Limited information	Chromatographic separation : **1** HRMS ion: **1,5** Accurate mass ≤ 5 ppm (values higher than 5 ppm could be allowed for Screening purposes)	Isotopic pattern Comparison to libraries/databases and considering a scoring	no
2. Full MS with Fragmentation / without precuror ion isolation	AIF (All Ion Fragmentation)	All Ion	x (target, suspect, non-target) Screening/Confirmation	Accurate mass ≤ 5 ppm	no	yes	Spetra of precursor ion and possible fragments	Available by comparison with libraries/database; Available depending on the evaluation software; Considered in scoring	Chromatographic separation : **1** HR-MS ion: **1,5** HR-MS* product ion [1]: **1,5** [-1] Accurate mass ≤ 5 ppm (values higher than 5 ppm are allowed for Screening) Accurate mass for fragment ions/ HR-MS ions ≤ 5 ppm (should also be considered) Isotopic pattern	Available by comparison with libraries/databases **QToF**: ion ratio available by using Quantification software For Qualification software: ion ratio considered in scoring	Chromatographic separation HR-MS ion For authorised substances at least 2 x HR-MSn product ions (*) For non-authorised substances at least 3 x HR-MSn product ions (*) Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of fragment ions (≤ 5 ppm) Isotopic pattern
		DDA Auto MSMS SVATH	x (suspect, non-target, target) Screening/(confirmation)	Accurate mass ≤ 5 ppm	no	yes	Spetra of precursor ion and possible fragments	Available by comparison with libraries/database; Available depending on the evaluation software; Considered in scoring	Chromatographic separation : 1 HR-MS ion: **1,5** HR-MSn product ion (*): **1,5** [-1] Accurate mass ≤ 5 ppm (values higher than 5 ppm are allowed for Screening) Accurate mass for fragment ions/ HR-MS ions ≤ 5 ppm (should also be considered) Isotopic pattern	Available by comparison with libraries/databases **QToF**: ion ratio available by using Quantification software For Qualification software: ion ratio considered in scoring	Chromatographic separation HR-MS ion For authorised substances at least 2 x HR-MSn product ions (*) For non-authorised substances at least 3 x HR-MSn product ions (*) Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of fragment ions (≤ 5 ppm) Isotopic pattern
		Data Independent Analysis (DIA)	x (target, suspect, non-target) Screening/Confirmation	Accurate mass ≤ 5 ppm	no	yes	Spetra of precursor ion and possible fragments	Available by comparison with libraries/database; Available depending on the evaluation software; Considered in scoring	Chromatographic separation : **1** HR-MS ion: **1,5** HR-MS* product ion [1]: **1,5** [-1] Accurate mass ≤ 5 ppm (values higher than 5 ppm are allowed for Screening) Accurate mass for fragment ions/ HR-MS ions ≤ 5 ppm (should also be considered) Isotopic pattern	Available by comparison with libraries/databases **QToF**: ion ratio available by using Quantification software For Qualification software: ion ratio considered in scoring	Chromatographic separation HR-MS ion For authorised substances at **least 2** x HR-MS* product ions [1] For non-authorised substances at **least 3** x HR-MS* product ions [1] Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of fragment ions (≤ 5 ppm) Isotopic pattern
	Full MS /ddMS² (Top n) without inclusion list		x (suspect, non-target) Screening/Confirmation	Accurate mass ≤ 5 ppm	no	yes	Spetra of precursor ion and possible fragments	Available by comparison with libraries/database; Available depending on the evaluation software; Considered in scoring	Chromatographic separation : **1** HR-MS ion: **1,5** HR-MS* product ion [1]: **1,5** [-1] Accurate mass ≤ 5 ppm (values higher than 5 ppm are allowed for Screening) Accurate mass for fragment ions/ HR-MS ions ≤ 5 ppm (should also be considered) Isotopic pattern	Available by comparison with a library/database **OrbiTrap**: ion ratio considered in scoring	Chromatographic separation HR-MS ion For authorised substances at **least 2** x HR-MS* product ions [1] For non-authorised substances at **least 3** x HR-MS* product ions [1] Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of fragment ions (≤ 5 ppm) Isotopic pattern
	Full MS /ddMS² (Top n) with inclusion list		x (target); Confirmation	Accurate mass ≤ 5 ppm	yes	yes	yes (full scan)	Available by comparison with libraries/database; Considered in scoring	Chromatographic separation : **1** HR-MS ion: **1,5** HR-MS* product ion [1]: **1,5** [-1] Accurate mass ≤ 5 ppm (values higher than 5 ppm are allowed only for Screening) Accurate mass for fragment ions/ HR-MS ions ≤ 5 ppm (should also be considered) Isotopic pattern	Considered by comparison with libraries/databases **OrbiTrap (TraceFinder)**: ion ratio considered in scoring	Chromatographic separation HR-MS ion For authorised substances at **least 2** x HR-MS* product ions [1] For non-authorised substances at **least 3** x HR-MS* product ions [1] Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of fragment ions (≤ 5 ppm) Isotopic pattern
	Data Independent Analysis (ₚDIA)		x (target, suspect, non-target) Screening/Confirmation	Accurate mass ≤ 5 ppm	no	yes	Spetra of precursor ion and possible fragments	Available by comparison with libraries/database; Available depending on the evaluation software; Considered in scoring	Chromatographic separation : 1 HR-MS ion: t,5 HR-MS* product ion [1]: **1,5** [-1] Accurate mass ≤ 5 ppm (values higher than 5 ppm are allowed for Screening) Accurate mass for fragment ions/ HR-MS ions ≤ 5 ppm (should also be considered) Isotopic pattern	Available in TraceFinder data evaluation	Chromatographic separation HR-MS ion For authorised substances at **least 2** x HR-MS* product ions [1] For non-authorised substances at **least 3** x HR-MS* product ions [1] Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of fragment ions (≤ 5 ppm) Isotopic pattern
3. Full MS with Fragmentation / with precursor ion isolation		Targeted MS/MS SVATH/MRM[HR] MRM[HR]	x (target, suspect); Confirmation	Accurate mass ≤ 5 ppm	yes	yes	yes (full scan)	yes	Chromatographic separation : **1** HR-MS ion: **1,5** HR-MSn product ion: **2,5** Accurate mass ≤ 5 (values higher than 5 ppm are allowed only for Screening) Accurate mass of fragment ions ≤ 5 (should also be considered)	Available in Quantitative data evaluation	Chromatographic separation HR-MS ion For authorised substances at **least 2** x HR-MS* product ion For non-authorised substances at **least 2** x HR-MS* product ions Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of product ions/fragment ions (≤ 5 ppm) Isotopic pattern
		DDA (Auto MS/MS) with inclusion list	x (target, suspect); Confirmation	Accurate mass ≤ 5 ppm	yes	yes	yes (full scan)	yes	Chromatographic separation : **1** HR-MS ion: **1,5** HR-MSn product ion (*): **2,5** Accurate mass ≤ 5 ppm (values higher than 5 ppm are allowed only for Screening) Accurate mass of fragment ions ≤ 5 ppm (should also be considered) Isotopic pattern	Available in Quantitative data evaluation	Chromatographic separation HR-MS ion For authorised substances at **least 2** x HR-MS* product ion For non-authorised substances at **least 2** x HR-MS* product ions Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of product ions/fragment ions (≤ 5 ppm) Isotopic pattern
	SIM, target SIM, multiplex SIM		x (target); Confirmation	Accurate mass ≤ 5 ppm	yes		yes (full scan)	yes	Chromatographic separation : **1** HR-MS ion: **1,5** HR-MS* product ion: **2,5** Accurate mass of precursor ion ≤ 5 ppm (values higher than 5 ppm are allowed only for Screening purposes) Accurate mass of fragment ions ≤ 5 ppm (should also be considered)	Available in TraceFinder data evaluation	Chromatographic separation HR-MS ion For authorised substances at **least 2** x HR-MS* product ion For non-authorised substances at **least 2** x HR-MS* product ions Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of product ions/fragment ions (≤ 5 ppm) Isotopic pattern
	PRM (Parallel Reaction Monitoring)		x (target); Confirmation	Accurate mass ≤ 5 ppm	yes		yes (full scan)	yes		Available in TraceFinder data evaluation	
	tSIM/ddMS²		x (target); Confirmation	Accurate mass ≤ 5 ppm	yes		yes (full scan)	yes		Available in TraceFinder data evaluation	

HRMS guidance

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1. Full MS (no fragmentation)
2. **Full MS with Fragmentation / without precursor ion isolation**
3. Full MS with Fragmentation / with precursor ion isolation

Orbitrap	QToF	Screening / Confirmation	Precursor selection	Fragments (traceable to a single precuror)	Isotopic pattern/Spectra	Spectra	Ion ratio
AIF (All Ion Fragmentation)	All Ion	x (target, suspect, non-target) Screening/Confirmation	Accurate mass ≤ 5 ppm	no	yes	Spetra of precursor ion and possible fragments	Available by comparison with libraries/database; Available depending on the evaluation software; Considered in scoring

Identification point CIR (EU) 2021/808	Relative intensities (ion ratio)	Confirmation by considering
Chromatographic separation : 1 HR-MS ion: 1,5 HR-MS^n product ion (*): 1,5 (•) Accurate mass ≤ 5 ppm (values higher than 5 ppm are allowed for Screening) Accurate mass for fragment ions/ HR-MS ions ≤ 5 ppm (should also be considered) Isotopic pattern	Available by comparison with libraries/databases **QToF**: ion ratio available by using Quantification software For Qualification software: ion ratio considered in scoring	Chromatographic separation HR-MS ion For authorised substances at least 2 x HR-MSn product ions (*) For non-authorised substances at least 3 x HR-MSn product ions (*) Accurate mass of precursor ion (≤ 5 ppm) Accurate masses of fragment ions (≤ 5 ppm) Isotopic pattern

CIR (EU) 2021/808 (consol. 17 February 2025)

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COMMISSION IMPLEMENTING REGULATION (EU) 2021/808

of 22 March 2021

1.2.1. General requirements for confirmatory methods

For prohibited or unauthorised substances, the **CCα shall be as low as reasonably achievable**. For prohibited or unauthorised substances, for which an RPA is established under Regulation (EU) 2019/1871 the CCα shall be lower than or equal to the reference point for action.

MMPR guidance

COMMISSION DELEGATED REGULATION (EU) 2022/1644

of 7 July 2022

ANNEX I

Group A – **Prohibited or unauthorised pharmacologically active substances** in food-producing animals

MMPR guidance

Co-funded by the European Union

Minimum Method Performance Requirement (MMPR)
Clarification of method requirements – "level of interest"

Laboratories should ensure :

CCβ for screening methods

CCα for confirmatory methods

< MMPR !

= > Introduction of default values for substance groups


Version 3.0
10 December 2025

European Union Reference Laboratories supported by the

Co-funded by the European Union

DRAFT

This document has not been developed by the European Commission. Any views expressed related to the interpretation of EU law may therefore not be regarded as stating an official position of the Commission. Only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

EURL GUIDANCE ON MINIMUM METHOD PERFORMANCE REQUIREMENTS (MMPRs) FOR SPECIFIC PHARMACOLOGICALLY ACTIVE SUBSTANCES IN SPECIFIC ANIMAL MATRICES

The purpose of this technical guidance is to improve and harmonise the performance of analytical methods used for the analysis of residues of unauthorised or prohibited pharmacologically active substances and for authorised pharmacologically active substances in matrices or species for which no use is authorised, taking into account state-of-the-art analytical methods.

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Specific rules for MMPR

All substances in table 1 of CR (EU) 37/2010 count as B-substances, also in case of "restrictions" e.g. for a species (an individual evaluation of consumer risks / health concerns has taken place)

Exception : Council Directive 96/22/EC substances ("ban of growth promoters")

Simplified rule for B-substances without MRL in a specific matrix or species:

the MMPR is 1/4th of the "cascade MRL"

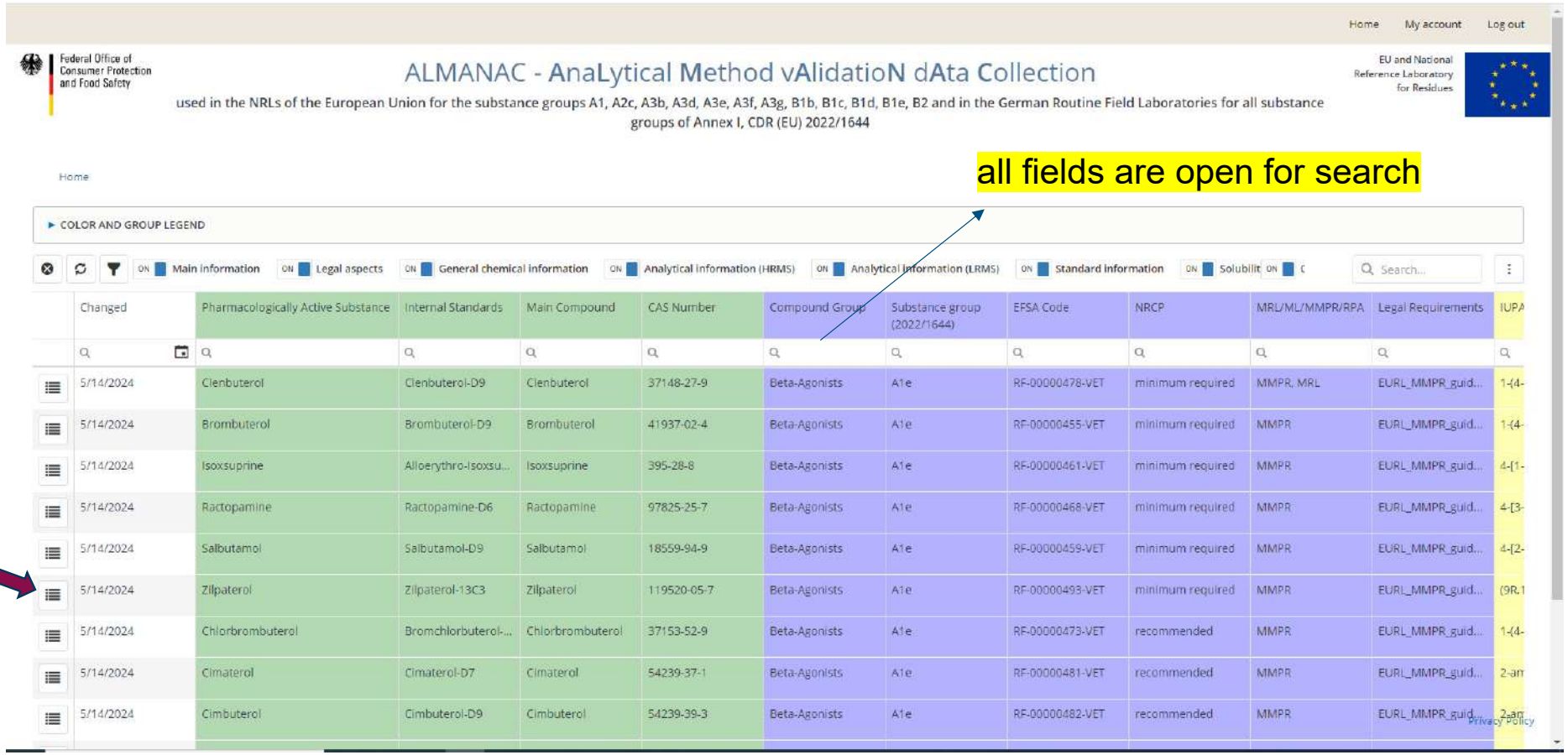
This requires in principle a spike level of down to 0.1 times the cascade MRL - where analytically feasible

The "cascade MRL" is based on European law (Regulation (EU) 2019/6 on veterinary medicinal products, Art. 113, 114) - Exceptional use of a medicinal product outside the terms of the marketing authorization under the direct personal responsibility of a veterinarian (to avoid causing unacceptable suffering of the animals)

Support in method devopment and validation

Co-funded by the European Union

Databases …



Substance data base and stability data base

Co-funded by the European Union

Main information

Legal aspects

Chemical informations

HRMS information

LRMS information

Standard information

Solubility, **stability** and contact

Pharmacologically Active Substance	Internal Standards	Main Compound	CAS Nu
Afoxolaner			
Chlorbrombuterol	Bromchlorbute		
Lotilaner			
Sotalol hydrochloride			
Sarolaner			
Zilpaterol			
Clenbuterol			
Isoxsuprine			
Cimaterol			
Cimbuterol			

Compound Group	Substance group (2022/1644)	EFSA Code	NRCP	MRL/ML/MM
			other	

IUPAC	SMILES Formula	InChI Key	Molecular Formula	Monoisotopic

m/z (LR)	MS/MS Transitions 1	MS/MS Transitions 2	MS/MS Transiti
425.9	138.0	195.9	
321.2	132.2	168.1	
595.9	165.9	496.9	
273.4	133.1	213.1	
480.9	115.1	415.9	
262.2	157.1	185.1	
277.3	132.1	168.1	
302.3	107.0	150.1	
220.3	143.1	160.2	
234.3	116.1	143.1	

Standard available	Standard name supplier (including salt etc)	CAS-number standard (e.g. salts)	Possible supplie
Yes	Afoxolaner	1093861-60-9	WITEGA Laboratorien
Yes	Bromoclenbuterol hydroc...	78982-84-0	WITEGA Laboratorien
Yes	Lotilaner	1369852-71-0	WITEGA Laboratorien
Yes	Sotalol hydrochloride	959-24-0	WITEGA Laboratorien
Yes	Sarolaner	1398609-39-6	WITEGA Laboratorien
Yes	Zilpaterol hydrochloride	119520-06-8	WITEGA Laboratorien
Yes	Clenbuterol hydrochloride	21898-19-1	Sigma-Aldrich Chemie
Yes	Isoxsuprine hydrochloride	579-56-6	Sigma-Aldrich Chemie
Yes	Cimaterol	54239-37-1	WITEGA Laboratorien
Yes	Cimbuterol	54239-39-3	WITEGA Laboratorien

m/z	Fragment 1	Fragment 2	Fragment 3
578			196.0390
629			303.0254
496			165.9955
			255.1162
223			129.0704
709			
449			20
913			284
602			
604			

Solubility	With Stability	Contact
Ethanol		BVL
Ethanol	1 year, -20 °C, 12,5...	BVL
Ethanol		BVL
Ethanol		BVL
Ethanol		BVL
Ethanol	1 year, -20 °C, 125 ...	BVL
Ethanol	1 year, -20 °C, 12,5...	BVL
Ethanol	1 year, -20 °C, 25 n...	BVL
Ethanol	1 year, -20 °C, 50 n...	BVL
Ethanol	1 year, -20 °C, 25 n...	BVL

EURL / NRL working group on stability

CIR (EU) 2021/808 (consol. 17 February 2025)

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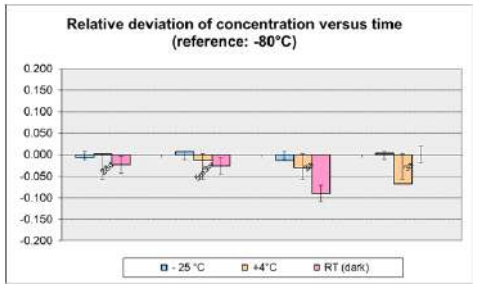
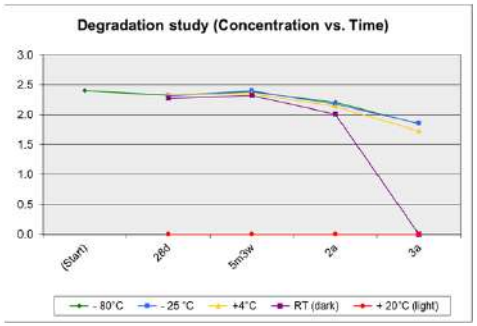
2.5. Stability

(…)If stability data for analytes in the matrix are available (e.g. on the basis of information from the EURLs, published data, etc.), **these data do not need to be determined by each laboratory**. However, referring to available stability data of analytes in solution and in matrix is only acceptable if **identical conditions** are applied.





EURL / NRL Working Group

- Suitable procedures for **stability data collection** (**who can submit data**, to whom shall data be submitted, **who checks data**, who decides which data is accepted, entry into platform, notification of submitting person)
- **Selection of data** for evaluation (quality criteria for acceptance)
- Presentation of stability data (types of graphs, csv)
- Requirements for a platform for presentation of stability data

= > **Guidance on stability studies** (available by the end of the year on the EURL website)

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Data collection - Import file

- **General information**
  - Substance
  - CAS No.
  - Data source (BVL, ...)
  - Date of submission
- **Study information**
  - Solution/Extract/Matrix/Other
  - Evaluation w regard to ISTD
  - Study endpoint
  - Vessel material (glass, polypropylene, de-activated glass, other plastic)
  - Study code (unique code for relating all individul results to a complete study
- **Storage conditions**
  - Temperatures
  - Storage Time
  - Storage Time Unit
  - Longest storage time of this study
  - Light/Dark
- Different entries depending on Matrix, Solution or Extract: e.g. incurred material, species, solvent component, sample preparation
- **Measurement**
  - Measurement Technique
  - No. of test portions per T-t combination
  - Results obtained using IS?
- **Method**
  - screening/confirmation
  - quant/semi-quant/qual
  - confirmation criteria were assessed y/n
- **Results**
  - results as area, ratio, concentration
  - results after storage confirmed/not confirmed
  - Numerical result (mean of all replicates per T-t combination)
  - repeatability/reproducibility std dev
  - Reference (fresh sol/matrix, reference T, initial measurement)
  - stability criterion

Outlook

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HRMS guidance	MMPR guidance	Substance data base and stability data base
1.2.4. Specific performance criteria for mass spectrometry 1.2.4.1. Mass spectrometric detection	1.2.1. General requirements for confirmatory methods	2.5. Stability 2.5.1. / 2.5.2 Determination of the stability of the analyte in solution / in matrix

https://pixnio.com/de/objekte/fernglas-makro-geraet

Availabilities

Guidance documents will be released in the 1st quarter of 2026

Substance data base is available (partly restricted access)

Stability data base in the course of 2026

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

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

WAGENINGEN UNIVERSITY & RESEARCH
100years

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Thank you for your interest !

Contact :

https://eurl-residues.eu/

...and our EURL teams for their contributions !