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Results of the proficiency test on plant protection products in 2021

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AMBIENTE E SALUTE

ISTITUTO SUPERIORE DI SANITÀ

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2021, v, 33 p. Rapporti ISTISAN 21/19

In 2021, the fourth Proficiency Test (PT) was organized among laboratories all over world on plant protection products available on the Italian market. The aim of the trial was to find out the quantity of active ingredient on the different formulation of the plant protection products. Eight Italian laboratories and seventeen worldwide laboratories, that routinely deal with pesticides, were invited to participate. Laboratories are not obligated to take part in the PT. Four Italian laboratories and thirteen worldwide laboratories sent their results. All laboratories obtained data with acceptable values of z-score within the limits $-3.5 \leq Z \leq +3.5$.

Key words: Proficiency test; Plant protection products; Imazamox; Fenhexamid; Trinexapc-ethyl

Istituto Superiore di Sanità
Risultati dell'esercizio interlaboratorio sui prodotti fitosanitari nel 2021.
Angela Santilio, Roberto Cammarata, Valentina Picardo
2021, v, 33 p. Rapporti ISTISAN 21/19 (in inglese)

Nel 2021 è stato organizzato il quarto esercizio interlaboratorio su prodotti fitosanitari disponibili sul mercato nazionale. L'esercizio riguardava la determinazione del contenuto di principio attivo presente in prodotti fitosanitari di diversa formulazione. Sono stati invitati a partecipare 8 laboratori italiani preposti al controllo dei prodotti fitosanitari e 17 laboratori mondiali interessati ai controlli sui prodotti fitosanitari. La partecipazione è su base volontaria e hanno aderito quattro laboratori italiani e tredici europei. Tutti i laboratori hanno ottenuto risultati con valori di z-score entro i limiti definiti $-3.5 \leq Z \leq +3.5$.

Parole chiave: Esercizio interlaboratorio; Prodotti fitosanitari; Imazamox; Fenhexamid; Trinexapac-ethyl

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ABBREVIATIONS

AFSCA	Agence fédérale pour la sécurité de la chaîne alimentaire (Federal Agency for the Safety of the Food Chain)
AAPCO	Association of American Pesticide Control Officials
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council
CS	Capsule Suspension
CV	Coefficient of Variation
DAD	Diode Array Detector
FID	Flame Ionisation Detector
GC	Gas Chromatography
HRMS	High Resolution Mass Spectrometry
ISO	International Organization for Standardization
ITPT	Italian Proficiency Test
LC	Liquid Chromatography
MAD	Median absolute deviation
MS	Mass Spectrometry
N/A	Not Available
PDA	PhotoDiode Array
PPP	Plant Protection Product
PPP01	Plant Protection Product number 1
PPP02	Plant Protection Product number 2
PPP03	Plant Protection Product number 3
PT	Proficiency Test
SC	Suspension Concentrate
SD	Standard Deviation
SL	Soluble Concentrate
UV	UltraViolet
VIS	Visible
VWD	Variable Wavelength Detector
z-score	Standard Score

Symbols

σ_P	standard deviation for proficiency test
T-test	statistic test of Student's t distribution

PREFACE

The European legislation on Plant Protection Products (PPPs) – Regulation (EC) 1107/2009) – regulates the authorisation, placing on the market, use and control of PPPs and of any active substances, safeners, synergists, co-formulants and adjuvants, which they might contain or which they might consist of.

The objective of those rules is to ensure a high level of protection of both human and animal health and of the environment through evaluation of the risks posed by PPPs, while improving the functioning of the Union market through harmonisation of the rules for their placing on the market and improving agricultural production.

In addition, the Regulation (EU) 2017/625 establishes a harmonised European Union framework for the organisation of official controls and official activities taking into account the rules on official controls laid down in Regulation (EC) 882/2004 and in relevant sectoral legislation, and the experience gained from the application of those rules.

The laboratories designated by the competent authorities to perform analyses on PPP samples taken in the context of official controls should possess the expertise, equipment, infrastructure and staff to carry out such tasks to the highest standards. To ensure sound and reliable results, those laboratories should be accredited for the use of these methods according to standard EN ISO/IEC 17025.

One of the instruments to reach a high-quality standard and performance is the participation in the interlaboratory test (Proficiency Test, PT) to demonstrate that the analytical data obtained from laboratories are reliable.

In the area of PPPs there are two organizations that plan PTs:

- Association of American Pesticide Control Officials (AAPCO)
  International organization that schedules PT on the active ingredient content on PPP on the basis of the American monitoring programmes;
- Agence Fédérale pour la Sécurité de la Chaîne Alimentaire (AFSCA)
  European organization that plans PT on physical chemical properties for PPPs.

For this reason, it is important to organize PTs for the active ingredient content for the national official laboratories.

This activity was planned in the framework of the collaboration with the Italian Ministry of Health and the Istituto Superiore di Sanità (ISS, the National Institute of Health in Italy).

As the national monitoring programs are in comply with the European monitoring ones, it is useful to enlarge the invitation to European Member State laboratories that work on this issue.

INTRODUCTION

In January 2021, all relevant Italian laboratories and European Member State laboratories were invited to participate in the 4th Italian PT on PPPs (later indicated as ITPT2021).

The announcement letter (Appendix A) was sent to the laboratories on 4th November 2020, according to the calendar the laboratories were asked to forward the invitation. The invitation was sent to 8 Italian laboratories and to 17 worldwide laboratories.

For the PT three different commercial products containing three active ingredients (Imazamox 7.62%; Fenhexamid 42.8%; Trinexapac-ethyl 11.30%) were shipped to the laboratories.

1. PROFICIENCY TEST ON PLANT PROTECTION PRODUCTS

1.1. Test materials

The test materials of the ITPT2021 consisted of three PPPs obtained from manufacturer and available from Italian market.

The product types are: Soluble Concentrate (SL), Suspension Concentrate (SC) and Capsule Suspension (CS) at a declared concentration reported in Table 1.

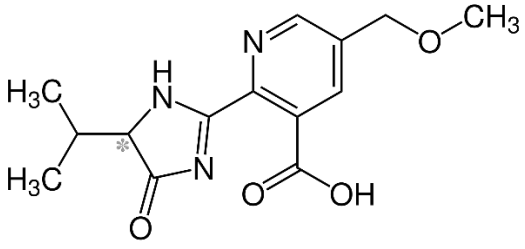
Table 1. Test materials of ITPT2020

Check Sample N.	Product description	Active ingredient	Declared level %
PPP01	Soluble Concentrate	Imazamox	7.62
PPP02	Suspension Concentrate	Fenhexamid	42.8
PPP03	Capsule Suspension	Trinexapac-ethyl	11.3

For the preparation of the subsamples to send each laboratories, the PPPs were mixed mechanically and shared in 17 samples for a total of 51 plastic containers sealed and stored at ambient temperature before the shipment to the participants. Each laboratory received three samples. Nothing was added to our samples.

1.2. Description of the active substances in the PPPs

1.2.1. Imazamox



IUPAC name
2-[(*RS*)4-Isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl]-5-methoxymethylnicotinic acid

Structure Formula $C_{15}H_{19}N_3O_4$

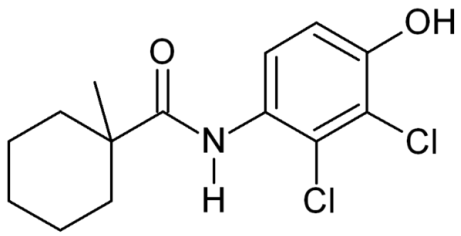
CAS number 114311-32-9

Imazamox is a racemic mixture with a molecular weight of 305.3 g/mol.

It is an imidazolinone herbicide which acts by inhibiting acetohydroxyacid synthase activity of unwanted vegetation, by the absorpion through both roots and foliage.

Imazamox is used as pre- or post- emergence herbicide, in particular the ammonium salt for the control of weeds in soy, maize, rape, alfalfa, peas and beans.

1.2.2. Fenhexamid



IUPAC name
N-(2,3-dichloro-4-hydroxyphenyl)-1-methylcyclohexane-1-carboxamide

Structure formula $C_{14}H_{17}Cl_2NO_2$

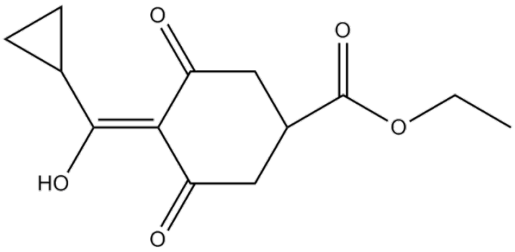
CAS number 126833-17-8

Fenhexamid is an aromatic amide with a molecular weight of 302.2 g/mol.

It is a sterol biosynthetis inibitor and an antifungal agrochemical. This fungicide acts with a non-systemic mechanism and, due to its low toxicity, on some crops.

Fenhexamid can be used up to one day before harvest, ensuring protection even in the post-harvest phase.

1.2.3. Trinexapac-ethyl



IUPAC name
ethyl 4-[cyclopropyl(hydroxy)methylidene]-3,5-dioxocyclohexane-1-carboxylate

Structure formula $C_{13}H_{16}O_5$

CAS number 95266-40-3

Trinexapac-ethyl is a plant growth regulator of grasses used to slow down their vegetative growth.

It is an ester with a molecular weight of 252.26 g/mol and it has known environmental transformation products that include the acid Trinexapac.

It allows to reduce the frequency of cuts and the amount of grass cut, respecting the aestethics of the turf.

1.3. Homogeneity and stability test

Homogeneity and stability tests were performed according to the ISO 13528:2015(E) - Annex B and the International Harmonized Protocol.

1.3.1. Homogeneity

Regarding the homogeneity test, ten bottles were randomly chosen and analysed in duplicate, in two different days.

Considering that the σ_{PT} is unknown, the statistically significant differences between PT items used were evaluated with the analysis of variance T-test at α=0.05, if the data series are more than two the Fisher Test is necessary. The T-test shows a significativity level (P) higher than 0.05 for

each active substance. It is possible to say the samples are not different one each other: they are homogeneous.

The results are shown in Table 2 for all compounds and the concentrations are in g/kg.

Table 2. Homogeneity results of the PT samples in g/kg (ITPT2021)

Sample ID	Imazamox		Fenhexamid		Trinexapac-ethyl	
	a	b	a	b	a	b
#1	70.9	72.7	404.7	367.4	115.1	122.7
#2	70.6	73.5	416.0	375.2	116.5	115.8
#3	71.2	73.2	423.1	421.7	113.6	100.8
#4	71.2	73.0	421.9	419.1	114.4	100.7
#5	70.1	72.7	424.2	428.0	111.6	111.8
#6	70.4	72.4	405.3	402.6	107.1	103.1
#7	69.9	72.0	409.3	407.9	104.6	95.9
#8	71.8	73.8	420.8	420.4	111.3	107.0
#9	69.7	71.8	414.4	409.1	106.2	94.1
#10	70.1	72.1	415.4	413.8	107.9	94.6
Mean	72.0	72.7	415.5	406.5	110.8	113.1
SD	1.62	0.64	6.99	19.5	4.04	11.7
t**	1.40		1.37		0.58	
P***	0.18		0.19		0.57	
Homogeneity	YES		YES		YES	

a, b: replicates of the same sample
t**: T of Student Test
P***: significativity level;
SD: Standard Deviation

1.3.2. Stability

The stability test was performed using two bottles, randomly chosen, which were analysed in duplicate in two occasions and each occasion twice:

- *Day 1*: before the shipment of the samples in January 2021;
- *Day 2*: at the deadline for reporting results in April 2021.

Stability test was judged acceptable as the percentage difference of concentration for each active substance was found less than 10%.

Table 3 shows the stability data of the ITPT2021.

Table 3. Summary of stability data in g/kg (ITPT2021)

Active Ingredient	January	April	Concentration
Imazamox	73.6	70.7	76.2
Fenhexamid	407.6	427.3	428
Trinexapac-ethyl	114.6	108.3	116.4

Tables 4, 5, and 6 show the individual results for each substance. The deviation calculated with reference to the 1st analysis and to the declared label show a deviation less than 10% for all substances. The products are stable.

Table 4. IMAZAMOX: results of stability test in g/kg (ITPT2021)

Parameter	January				April			
	Replicate 1		Replicate 2		Replicate 1		Replicate 2	
	inj 1	inj 2	inj 1	inj 2	inj 1	inj 2	inj 1	inj 2
Sample 1	75.0	73.0	73.6	73.8	69.1	69.0	73.2	71.8
Sample 2	72.6	72.7	74.0	73.8	69.4	69.4	71.6	71.8
Mean	73.3		73.8		69.2		72.1	
SD	1.11		0.18		0.20		0.77	
Mean of 2 days	73.6				70.7			
Standard Deviation of 2 days	0.35				2.05			
Deviation (ref 1st Analysis)/ [(M2-M1)/M1]*100	-3.94							
Deviation (ref to declared label g/kg)/ [(SM-76.2)/76.2]*100	-5.25							
Stability Mean	72.2		Declared Label g/kg		76.2			
Stability Standard Deviation	1.20		CV %		1.66			

Table 5. FENHEXAMID: results of stability test in g/kg (ITPT2021)

Parameter	January				April			
	Replicate 1		Replicate 2		Replicate 1		Replicate 2	
	inj 1	inj 2	inj 1	inj 2	inj 1	inj 2	inj 1	inj 2
Sample 1	394.0	392.5	387.0	387.7	426.0	426.1	419.7	419.7
Sample 2	427.2	427.3	421.7	421.5	426.9	427.0	436.3	436.7
Mean	410.6		404.5		426.5		428.1	
SD	20.0		19.8		0.51		9.70	
Mean of 2 days	407.6				427.3			
Standard Deviation of 2 days	4.31				1.13			
Deviation (ref 1st Analysis)/ [(M2-M1)/M1]*100	4.83							
Deviation (ref to declared label g/kg)/ [(SM-428)/428]*100	-2.45							
Stability Mean	417.5		Declared Label g/kg		428			
Stability Standard Deviation	2.25		CV %		0.54			

Table 6. TRINEXAPAC-ETHYL: results of stability test in g/kg (ITPT2021)

Parameter	January				April			
	Replicate 1		Replicate 2		Replicate 1		Replicate 2	
	inj 1	inj 2	inj 1	inj 2	inj 1	inj 2	inj 1	inj 2
Sample 1	114.2	108.9	116.4	112.6	100.4	111.1	111.1	105.3
Sample 2	117.4	112.4	118.6	116.4	110.4	114.8	107.7	105.9
Mean	113.0		116.2		109.2		107.5	
SD	3.18		2.66		6.15		2.60	
Mean of 2 days	114.6				108.3			
Standard Deviation of 2 days	0.37				1.20			
Deviation (ref 1st Analysis)/ [(M2-M1)/M1]*100	-5.50							
Deviation (ref to declared label g/kg)/ [(SM-116.4)/116.4]*100	-4.21							
Stability Mean	111.5		Declared Label g/kg		116.4			
Stability Standard Deviation	0.59		CV %		0.53			

1.4. Distribution of the samples and instructions for the participants

Three plastic transparent containers with red cup were filled. Each sample was shipped to the participating laboratories at ambient temperature. An information message was sent out by e-mail during shipment so that laboratories make their own arrangements for the reception of the package, and a protocol was sent by e-mail.

The participants (Appendix B) were asked:

– to inform on the safe recipient of the samples in their laboratories;
– to report results in the appropriate form and send them to the organizer by e-mail along with the details of methodology used.

The samples were sent to the participant on 15th January 2021.

The deadline for results was 30th of April 2021.

The final report was dispatched to all participant at the end of July 2021.

1.5. Statistical evaluation of results

This PT has been evaluated using the modified z-score parameter to rate the laboratory performance for each active substance according to AAPCO protocol.

The outliers were calculated using the modified z-score.

1.5.1. Robust mean

The purpose of using a robust estimator for the mean was to cope with the possibility of outlying data points without having to remove them from the sample.

The robust mean estimator used was the median.

1.5.2. Robust estimate of standard deviation

The robust estimate of the standard deviation used was the MAD_E value.

To obtain the MAD_E, calculate Median Absolute Deviation (MAD) from the sample median:

$$MAD = median\ (|X_i - median\ (Xi)|_{i=1,2\ldots n})$$

Calculate MAD_E:

$$MAD_E = K \times MAD$$

For normally distributed data, K= 1.483:

$$MAD_E = 1.483 \times MAD$$

1.5.3. Calculation of modified z-scores

Modified z-scores (Zi) for each laboratory were calculated as:

$$Zi = 0.6745 \times {}^{(Xi\ -\ median)} / MAD$$

Z values falling outside the range of $-3.5 \leq Zi \leq 3.5$ were marked as outliers.

1.5.4. Presentation of data

Data is presented graphically in two ways:

– a scatter plot showing each participating laboratory's two-day mean value for each analyte along with the associated standard deviation. These plots also show the upper and lower Horwitz (Thompson) limits for the sample, as well as median ±2 MAD_E.

– a plot of modified z-scores.

2. ANALYSIS OF THE SUBSTANCES

Description and statistical evaluation of the results are presented for each compound separately. This year we decide to not apply Horwitz theorem, because the active substances concentrations are high enough to make it unnecessary.

2.1. Imazamox

Regarding the active substance Imazamox, 17 boxes were sent to all over the world, in particular 4 to Italian's Laboratories and 13 to European Laboratories outside Italy. They have been received 16 participation results; the one Laboratory missing is from Germany.

All the laboratories used for the analysis an LC instrument: 15 of them with a UV Detector and just 1 with a MS Detector. It is interesting to note that almost all of the laboratories choose to use an in-house method and just two applied a manufacturer's method, as is shown in Table 10. At the same time, all the methods gave appreciable data.

Table 10. IMAZAMOX: methods applied for analysis (ITPT2021)

Laboratories	In-House	CIPAC	Manufacturer's
Number	14	0	2

On the collected data it was applied a statistical evaluation based on a robust estimator (median) instead the mean. The purpose of this choose was to cope the possibility of outlying data points without having to remove them, so it was used the median and the standard deviation.

Figure 1 shows the lab's values of modified Z-score. The results obtained are laudable data, in fact all of them are inside the modified z-score range of $-3.5 \leq Z \leq +3.5$.

Two laboratories obtained an excellent value of modified z-score of 0.

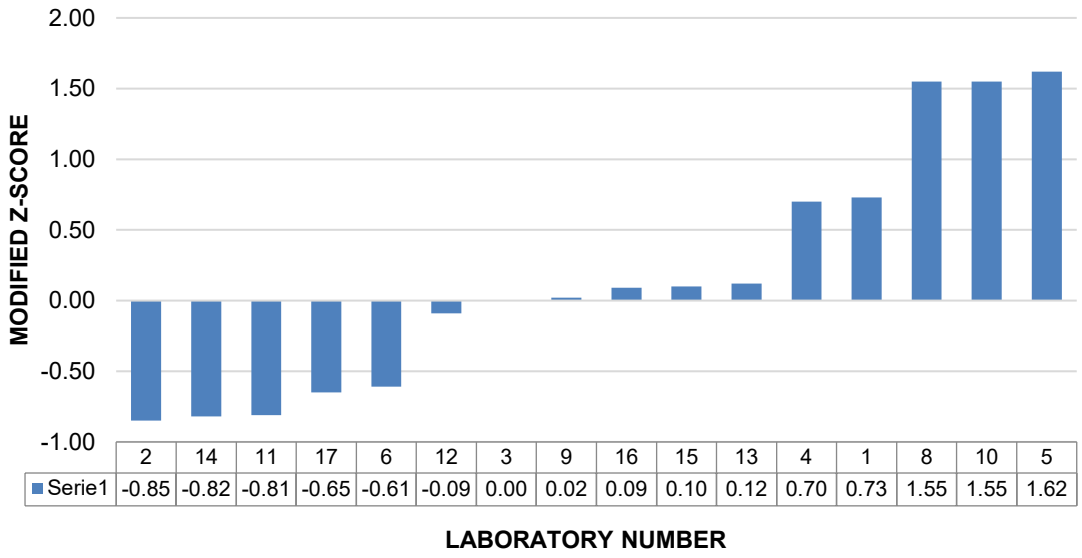


Figure 1. IMAZAMOX: modified z-scores (ITPT2021)

2.2. Fenhexamid

For the active substance Fenhexamid, 17 boxes were sent to all over the world, in particular 4 to Italian's Laboratories and 13 to European Laboratories outside Italy. They have been received 15 participation results. Fourteen laboratories used for the analysis an LC instrument and one the GC: 13 of them with a UV Detector, 1 with an FID Detector and 1 with a MS Detector.

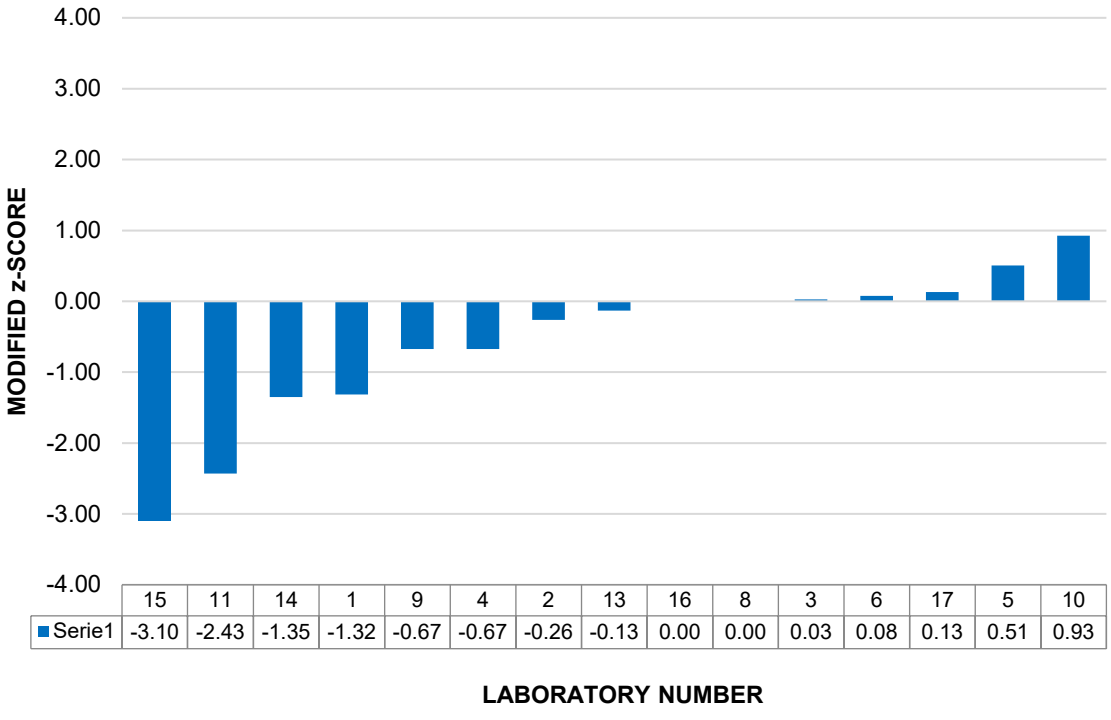
To carry out this analysis 11 laboratories applied an in-house method, 2 the CIPAC method and 2 used the manufacturer's method, as is showed in Table 11. At the same time, all the methods gave appreciable data, as Figure 2 shows.

Table 11. FENHEXAMID: methods applied for analysis (ITPT2021)

Laboratories	In-House	CIPAC	Manufacturer's
Number	11	2	2

As for the Fenhexamid, on the collected data it was applied a statistical evaluation based on a robust estimator instead the mean. The purpose of this choose was to cope the possibility of outlying data points without having to remove them, so it was used the median and the standard deviation. Figure 2 shows the lab's values of modified z-score. The results obtained are valuable data, in fact all of them are inside the z-score range of $-3.5 \leq Z \leq +3.5$.

Three laboratories obtained the excellent value of modified z-score of 0.



	15	11	14	1	9	4	2	13	16	8	3	6	17	5	10
Serie1	-3.10	-2.43	-1.35	-1.32	-0.67	-0.67	-0.26	-0.13	0.00	0.00	0.03	0.08	0.13	0.51	0.93

Figure 2. FENHEXAMID: modified z-scores (ITPT2021)

2.3. Trinexapac-ethyl

Trinexapac-ethyl was the last active substance and, as the other two, 17 boxes were sent to all over the world, in particular 4 to Italian's Laboratories and 13 to European Laboratories outside Italy. They have been received 16 participation results; the laboratory missing is from Italy. The analysis was performed using LC instrument for 12 laboratories and the other 4 decide to use the GC: 12 of them with a UV Detector and 4 with FID Detector. Thirteen laboratories choose to use an In-house method, others three a manufacturer's method, as is showed in Table 12. At the same time, all the methods gave appreciable data.

Table 12. FLUDIOXONIL: methods applied for analysis (ITPT2020)

Laboratories	In-House	CIPAC	Manufacturer's
Number	13	0	3

As for the other two active substances mentioned before, on the collected data it was applied a statistical evaluation based on a robust estimator (median) instead the mean. The purpose of this choose was to cope the possibility of outlying data points without having to remove them, so it was used the median and the standard deviation.

Figure 3 shows the lab's values of modified z-score. The results obtained are valuable data, in fact all of them are inside the z-score range of $-3.5 \leq Z \leq +3.5$.

One laboratory obtained the excellent value of modified z-score of 0.

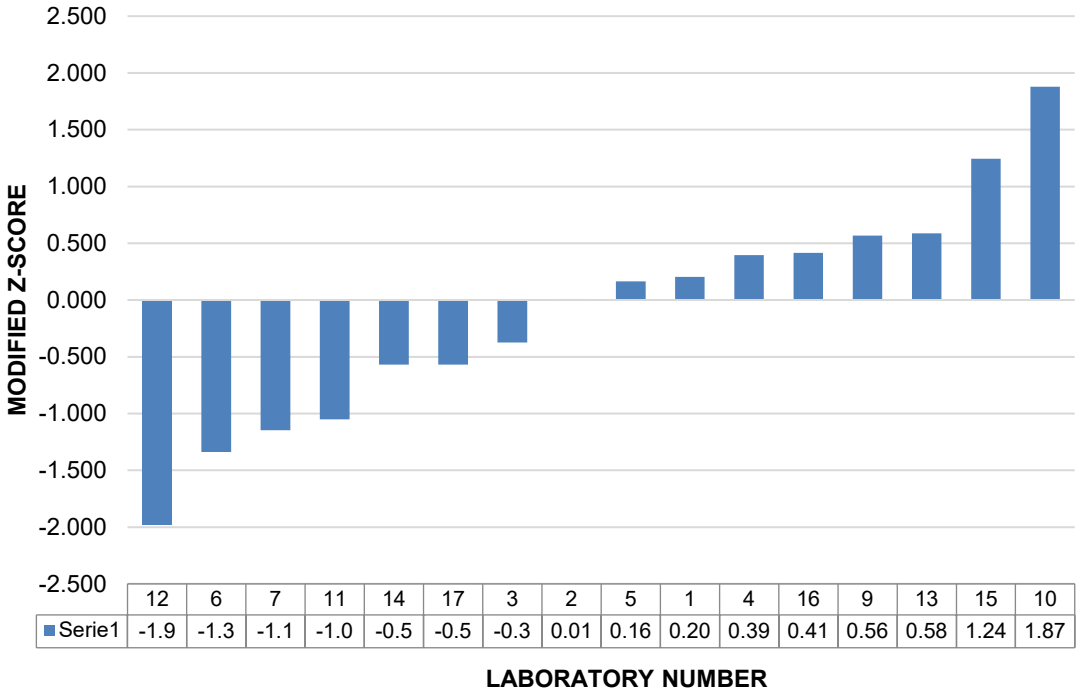


Figure 3. TRINEXAPAC-ETHYL: modified z-scores (ITPT2021)

3. RESULTS

The outcome of the ITPT2021 can be considered satisfactory due to the fourth PT organized by Italy.

The participation of the Italian and European laboratories was good. For Italy, four laboratories participated distributed as two of the north, one in central and one in the south of the Country. The European laboratories were thirteen, excluding Italy, distributed all in Europe.

The performance of the laboratories expressed in terms of modified z-score was satisfactory by almost all participants for all substances. For each active substance, there are not outlier values.

Almost all of the laboratories preferred to use an in-house method, inspired from the CIPAC and adapted to their lab conditions so with some modification, for example, without using the internal standard.

Tables 16, 17 and 18 summarize the participation per active ingredient and the results per active ingredient including and excluding the outliers.

For each active substance there were a percentage of failing results obtained with the modified z-score, as Table 16 shows.

Table 16. Summary of participation per active ingredient (ITPT2021)

ID Sample	Product description	Active ingredient	Participants (n.)	Labs using GC (n.)	Labs using LC (n.)	Failing results[1](%)
PPP01	Soluble Concentrate	Imazamox	16	0	16	0
PPP02	Suspencion Concentrate	Fenhexamid	15	1	14	0
PPP03	Capsule Suspencion	Trinexapac-ethyl	16	4	12	0

[1] Where failing indicates a mean assay result outside the modified z-score defined acceptable limits.

Table 17. Summary of lab results per active ingredient, including outliers (ITPT2021)

ID Sample	Analyte (Label claim)	Minimum result	Maximum result	Grand Average	Grand %CV
PPP01	Imazamox 7.62%	7.08	7.98	7.37	3.47
PPP02	Fenhexamid 42.8%	38.3	50.4	42.4	7.20
PPP03	Trinexapac-ethyl 11.3%	10.6	11.8	11.1	2.50

Table 18. Summary of lab results per active ingredient, excluding outliers (ITPT2021)

ID Sample	Analyte (Label claim)	N. of outliers[1]	Average excluding outliers	%CV excluding outliers
PPP01	Imazamox 7.62%	0	7.37	3.47
PPP02	Fenhexamid 42.8%	0	42.4	3.80
PPP03	Trinexapac-ethyl 11.3%	0	11.1	2.50

[1] An outlier is flagged when the modified z-score falls outside the range of $-3.5 \leq Zi \leq 3.5$; see Appendix for calculations.

The performance by almost the laboratories expressed in terms of modified z-score was satisfactory for all substances. For each active substance, there are not outlier values.

Almost all of the laboratories used in-house methods, inspired from the CIPAC and adapted to their laboratories conditions so with some modification, for example, without using the internal standard.

Based on the results, it can be concluded that the PT was successfully organized and we are very glad to say a satisfactory number of people took part with all the inconvenient of this year and we run out our fourth edition!

Details of the z-score values for each laboratory are given in Tables 19, 20 and 21 with the analytical technique used for each substance.

Table 19. IMAZAMOX Sample PPP01: summary results (ITPT2021)

ID Lab	Analytical technique	Two day average[1]	RPD[1]	Modified z- score[2]	Outlier[2]
1	HPLC-UV	7.54	0.00	0.73	NO
2	LC-DAD	7.08	-0.42	-0.85	NO
3	LC-UV	7.33	0.68	0.00	NO
4	HPLC-DAD	7.53	1.86	0.70	NO
5	HPLC-DAD	7.80	0.77	1.62	NO
6	LC-DAD	7.15	0.70	-0.31	NO
8	LC-HRMS	7.78	0.26	1.55	NO
9	HPLC-DAD	7.33	0.55	0.02	NO
10	HPLC-DAD	7.78	5.14	1.55	NO
11	LC-PhotoDA	7.09	0.07	-0.81	NO
12	LC-DAD	7.30	1.37	-0.09	NO
13	HPLC-DAD UV VIS	7.36	-0.82	0.12	NO
14	LC-DAD	7.09	0.14	-0.82	NO
15	LC-DAD	7.30	1.23	-0.10	NO
16	HPLC-VWD	7.35	-0.82	0.09	NO
17	LC-PhotoDA	7.14	-0.14	-0.65	NO

Grand Average[3]	7.37
Total SD	0.26
Total Median[4]	7.33
MAD	0.002
MAD_E	0.003

[1] Average yield and Relative Percent Difference between the two-day determinations per laboratory.
[2] An outlier is flagged when the modified z-score falls outside the range of $-3.5 \leq Zi \leq 3.5$; see Glossary.
[3] Grand average, standard deviation and median.
[4] Median Absolute Deviation Robust estimate of standard deviation; see Glossary for calculations.

Table 20. FENHEXAMID Sample PPP02: summary results (ITPT2021)

ID Lab	Analytical technique	Two day average[1]	RPD[1]	Modified z-score[2]	Outlier[2]
1	HPLC-UV	42.5	0.47	-0.27	NO
2	LC-DAD	42.8	-0.47	-0.13	NO
3	LC-UV	43.2	-0.46	0.67	NO
4	HPLC-DAD	42.7	-4.22	-0.00	NO
5	HPLC-DAD	42.6	-1.18	-0.13	NO
6	LC-DAD	43.5	-1.15	1.01	NO
8	LC-HRMS	42.9	0.12	0.33	NO
9	HPLC-DAD	42.5	0.09	-0.27	NO
10	HPLC-DAD	42.9	-1.17	0.13	NO
11	UHPLC-PhotoDA	40.9	-1.34	-2.43	NO
13	GC-FID	42.9	0.00	0.27	NO
14	LC-DAD	42.1	-1.19	-0.78	NO
15	LC-DAD	40.4	-10.4	-3.10	NO
16	HPLC-VWD	42.9	1.37	0.29	NO
17	LC-PhotoDA	42.0	-2.86	-0.94	NO

Grand Average[3]	42.4
Total SD	0.90
Total Median[4]	42.7
MAD	0.00
MAD_E	0.01

[1] Average yield and Relative Percent Difference between the two-day determinations per laboratory.
[2] An outlier is flagged when the modified z-score falls outside the range of $-3.5 \leq Zi \leq 3.5$; see Glossary.
[3] Grand average, standard deviation and median.
[4] Median Absolute Deviation Robust estimate of standard deviation; see Glossary for calculations.

Table 21. TRINEXAPAC-ETHYL sample PPP03: summary results (ITPT2021)

ID Lab	Analytical technique	Two day average[1]	RPD[1]	Modified z-score[2]	Outlier[2]
1	HPLC-UV	11.2	0.00	0.20	NO
2	LC-DAD	11.2	0.90	0.01	NO
3	LC-UV	11.1	-0.90	-0.38	NO
4	HPLC-DAD	11.3	4.44	0.39	NO
5	HPLC-DAD	11.2	1.07	0.16	NO
6	LC-DAD	10.8	1.85	-1.34	NO
7	GC-FID	10.9	0.92	-1.15	NO
9	HPLC-DAD	11.3	0.09	0.57	NO
10	GC-FID	11.6	-0.09	1.88	NO
11	LC-PhotoDA	10.9	0.28	-1.05	NO
12	LC-DAD	10.6	1.22	-1.98	NO
13	HPLC-DAD	11.3	0.00	0.59	NO
14	LC-DAD	11.0	-0.36	-0.57	NO
15	GC-FID	11.5	-4.88	1.24	NO
16	GC-FID	11.3	2.40	0.41	NO
17	LC-PhotoDA	11.0	1.82	-0.57	NO

Grand Average[3]	11.1
Total SD	0.28
Total Median[4]	11.1
MAD	0.002
MAD_E	0.003

[1] Average yield and Relative Percent Difference between the two-day determinations per laboratory.
[2] An outlier is flagged when the modified z-score falls outside the range of $-3.5 \leq Zi \leq 3.5$; see Glossary.
[3] Grand average, standard deviation and median.
[4] Median Absolute Deviation Robust estimate of standard deviation; see Glossary for calculations.

Table 25, 26 and 27 report the information on analytical methods used for each substance and each laboratory.

Table 25. IMAZAMOX: representative method for the determination (ITPT2021)

ID Lab	Reference method	Internal standard	Extractants	Sample preparation	Injection volume	Column T°	Detector	Column
1	In-house method	N/A	Acetonitrile	Sonicate for 15 min. Filter through a 0.45 µm filter	5 µL	ambient	Dionex UVD 170S	Zorbax SB-C18 5 µm, 4.6 mm × 250 mm
2	In-house method	N/A	Acetonitrile	Sonicate for 8 min. Filter through 0.22 µm PTFE syringe filter	0.5 µL	25°C	DAD	Phenomenex Kinetix C18 2.6 µm, 100 mm × 2.1 mm
3	In-house method	N/A	Acetonitrile	Sonicate for 15 min	2 µL	30°C	UV	XTerra RP18 3.5 µm, 150 mm × 2.1 mm
4	In-house method	N/A	Water:Acetonitrile (10:90 v/v)	Ultrasonicate 15 min. Dilute and filter with 0.45 µm PTFE	10 µL	30 °C	DAD	Kintex C18 5 µm, 150 mm × 4.6 mm
5	In-house method	N/A	Acetonitrile	Dilute in 100 mL volumetric flasks with ACN	10 µL	35°C	DAD	NUCLEODUR C18 Gravity 5 µm, 150 mm × 4.6 mm
6	In-house method	N/A	Acidified water / Tetrahydrofuran (50/50 (v/v))	Sonicate for 15 min. Shake for homogenization. Filter through 0.2 µm PP disk	10 µL	35°C	DAD	Kromasil C8 5 µm, 150 mm × 4.6 mm
8	In-house method	N/A	Water:Methanol (10:90 v/v)	Dissolve sample in 5 mL of water. Fill to mark with methanol. Dilute with methanol and filter 0.45	20 µL	25°C	HRMS	Synergy 4µm Hydro-RP 80 Å 4 µm, 150 mm × 2 mm
9	In house method	N/A	Acetonitrile	Ultrasonic 20 min	5 µL	40°C	DAD	ZORBAX ODS 5 µm, 4.6 mm × 150 mm
10	In house method	N/A	N/A	Weight sample and dilute 25 mL ACN. Take 1 mL of sample to 10 mL mobile phase	10 µL	none	DAD	Zorbax Eclipse Plus C18 5 µm, 4.6 mm × 250 mm
11	In-house method	N/A	Acetonitrile	Weigh 350 mg sample into a 50 mL measuring flask. Ultrasonicate for 5 min, fill to the mark at 20°C with acetonitrile. Filter through a 0.45 µm PTFE filter	2 µL	40°C	PhotoDA	Agilent Poroshell 120 SB-C18 2.7 µm, 4.6 mm i.d. × 100 mm

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ID Lab	Reference method	Internal standard	Extractants	Sample preparation	Injection volume	Column T°	Detector	Column
12	In-house method	N/A	Acetonitrile	Sonicate for 15 min. Dilute and filter through 0.45 um nylon disk	10 µL	35°C	DAD	Agilent Zorbax Eclipse XDB C8 5 µm, 150 mm × 4.6 mm
13	In house method	N/A	Water: Methanol (10:90 v/v)	Add water. Sonicate for 10 s. Add methanol to the mark. Homogenize and equilibrate to the room temperature	2 µL	40°C	DAD UV VIS	Phenomenex Gemini NX C18 3 µm, 150 mm × 4.6 mm
14	Manufacturer's method	N/A	Water:Acetonitrile (20:80 v/v)	Sonicate for 5 min. Shake for 1 min and filter through 0.45 µm nylon disk	10 µL	40°C	DAD	Phenomenex Gemini C18 5 µm, 150 mm × 4.6 mm
15	Manufacturer's method	N/A	Acetonitrile	Transfer a quantity of the homogeneous sample containing about 100 mg of active substance to a volumetric flask (100 mL), add 50 mL of acetonitrile. Ultrasonicate for 5 min. Wait until the temperature is stabilized and fill to mark with acetonitrile. Take 5 mL of this solution and dilute to a final volume of 50 mL with acetonitrile. Filter before to inject	10 µL	25°C	DAD	Zorbax eclipse C18 5µm, 250 mm × 4.6 mm
16	In-house method	N/A	Acetonitrile	Sonicate for 10 min. Filter through Nylon 0.45 µm disk	5 µL	30°C	VWD	ZORBAX Eclipse, XDB-C18 5 µm, 250 mm × 4.6 mm
17	In-house method	N/A	Acetonitrile	Weigh, dilute in acetonitrile to volume	5 µL	25°C	PhotoDA	Phenomenex Kinetix C18 2.6 µm, 100 mm × 2.1 mm

Table 26. FENHEXAMID: representative method for the determination (ITPT2021)

ID Lab	Reference method	Internal standard	Extractants	Sample preparation	Injection volume	Column T°	Detector	Column
1	In-house method	N/A	Acetonitrile	Sonicate for 15 min, filter 0.45 µm	5 µL	ambient	Dionex UVD 170S	Zorbax SB-C18 5 µm, 4.6 mm × 250 mm
2	In-house method	N/A	Acetonitrile: Water (90:10 v/v)	Sonicate for 8 min, filter through 0.22 µm PTFE syringe filter	0.5 µL	25° C	DAD	Phenomenex Kinetex C18 2.6 µm, 100 mm × 2.1 mm
3	In-house method	N/A	Acetonitrile	Sonicate for 15 min	2 µL	30° C	UV	XTerra RP18 3.5 µm, 150 mm × 2.1 mm
4	In-house method	N/A	Methanol	Ultrasonicate for 15 min, dilute and filter with 0.45 µm PTFE	10 µL	30° C	DAD	Kintex C18 5 µm, 150 mm × 4.6 mm
5	In-house method	N/A	Acetonitrile	Dilute in 100 mL volumetric flasks with ACN	10 µL	35° C	DAD	Phenomenex Luna C18 5µm, 250 mm × 4.6 mm
6	In-house method	N/A	Acidified water / Tetrahydrofuran (50/50 (v/v))	Sonicate for 15 mins, shake for homogenization. Filter through 0.2 µm PP disk	10 µL	35° C	DAD	Accucore Thermo 4 µm, 250 mm × 3 mm
8	In-house method	N/A	Water: Methanol (10:90 v/v)	Dissolve sample in 5 mL of water. Fill to mark with methanol. Dilute with methanol and filter 0.45 µm	20 µL	25°C	HRMS	Synergy 4µm Hydro-RP 80 Å 4 µm, 150 mm × 2 mm
9	In-house method	N/A	THF	Ultrasonicate for 30 min. Filter 0.45 µm PTFE disk	5 µL	40°C	DAD	ZORBAX ODS 5 µm, 4.6 mm × 150 mm
10	Manufacturer's method	N/A	Acetonitrile	Weigh and dilute in 50 mL ACN	10 µL	none	DAD	Zorbax Eclipse Plus C18 5 .0 µm, 4.6 mm × 250 mm
11	CIPAC UHPLC	N/A	Acetonitrile	Weigh 55 mg sample into a 200 mL measuring flask. Add 10 mL water and acetonitrile Ultrasonicate until complete dissolution. Fill to the mark at 20°C with acetonitrile. Filter through a 0.2 µm PTFE filter	0.5 µL	30°C	PhotoDA	Waters Acquity UPLC BEH C18 1.7 µm, 2.1 mm i.d. × 100 mm

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ID Lab	Reference method	Internal standard	Extractants	Sample preparation	Injection volume	Column T°	Detector	Column
13	In-house method	Dicyclohexyl phthalate 0.500 g/mL	Acetone	Sonicate for 5 min, shake for 5 seconds, filter through 0.45 µm nylon disk	1 µL	270°C	FID	Phenomenex ZB-5HT 30 m × 0.25 mm, 0.25 µm
14	CIPAC	N/A	Acetonitrile:Water (80:20 v/v)	Add 2 mL of water and shake to homogenize. Add extraction solvent and sonicate for 15 min. Dilute 1/10 with extraction solvent. Filter through 0.45 µm nylon disk	10 µL	40°C	DAD	Phenomenex Gemini C18 5 µm, 4.6 mm × 150 mm
15	Manufacturer's method	N/A	Acetonitrile	Transfer a quantity of the homogeneous sample containing about 50 mg of active substance to a volumetric flask, add 50 mL of acetonitrile. Ultrasonic bath for 15 minutes. Wait until the temperature is stabilized and fill to mark with acetonitrile. Filter before to inject.	10 µL	40°C	DAD	Lichrospher RP-18 5 mm, 250 mm x 4 mm
16	In-house method	N/A	Acetonitrile	Sonicate for 10 min. Filter through Nylon 0.45 µm disk	5 µL	30° C	VWD	ZORBAX Eclipse, XDB-C18 5 µm, 4.6 mm × 250 mm
17	In-house method	N/A	Acetonitrile	Weigh, disperse in 10 mL water, dilute in acetonitrile to volume	5 µL	25°C	PhotoDA	Phenomenex Kinetex C18 2.6 µm, 100 mm × 4.6 mm

Table 27. TRINEXAPAC ETHYL: representative method for the determination (ITPT2021)

ID Lab	Reference method	Internal standard	Extractants	Sample preparation	Injection volume	Column T°	Detector	Column
1	In-house method	N/A	Acetonitrile	Sonicate for 15 min. Filter through a 0.45 µm filter	5 µL	ambient	Dionex UVD 170S	Zorbax SB-C18 5 µm, 4.6 mm × 250 mm
2	In-house method	N/A	Acetonitrile	Sonicate for 8 min. Filter through 0.22 µm PTFE syringe filter	0.5 µL	25°C	DAD	Phenomenex Kinetix C18 2.6 µm, 100 mm × 2.1 mm
3	In-house method	N/A	Acetonitrile	Sonicate 15 min	2 µL	30°C	UV	XTerra RP18 3.5 µm, 150 mm × 2.1 mm
4	In-house method	N/A	Water:Acetonitrile (10:90 v/v)	Ultrasonicate for 15 min. Dilute and filter with 0.45 µm PTFE	10µL	30°C	DAD	Kintex C18 5 µm, 150 mm × 4.6 mm
5	In-house method	N/A	Acetonitrile	Dilute in 100 mL volumetric flasks with ACN and further dilute 10 mL to 50 mL volumetric flask with mobile phase: 100% ACN (550 mL) + 0.1% H_3PO_4 in water (450 mL)	10µL	30°C	DAD	Phenomenex Luna C18 5 µm, 250 mm × 4.6 mm
6	In-house method	N/A	Acidified water / Tetrahydrofuran (50/50 (v/v)) 10:90	Sonicate for 15 min. Shake for homogenization. Filter through 0.2 µm PP disk	10 µL	35°C	DAD	Accucore Thermo 4 µm, 250 mm × 3 mm
7	In-house method	N/A	Acetone	Dilute in 50 mL acetone. Sonicate for 15 min	1 µL	250°C	FID	Zebron/HM-G-006 DB17-01 30 m × 0.32 mm × 0.25 µm
9	In-house method	N/A	Acetonitrile	Ultrasonicate for 20 min. Filter 0.45 µm PTFE disk	5 µL	40°C	DAD	LUNA 3u C18 3 µm, 4.6 mm × 150 mm
10	Manufacturer's method	Di-n-propyl phthalate 3 mg/mL	Acetone	Weight sample. Add 25 mL IS	1 µL	325°C	FID	Thermo 30 m × 0.25 mm × 0.25 µm

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ID Lab	Reference method	Internal standard	Extractants	Sample preparation	Injection volume	Column T°	Detector	Column
11	In-house method	N/A	Acetonitrile	Weigh 320 mg sample into a 100 mL measuring flask. Dissolve and fill to the mark at 20°C with acetonitrile. Dilute 5 times in acetonitrile. Filter through a 0.45 µm PTFE filter	10 µL	30°C	PhotoDA	ZORBAX SB-C18 5 µm, 4.6 mm i.d. × 250 mm
12	In-house method	N/A	Acetonitrile	Sonicate for 15 minutes. Dilute and filter through 0.45 um nylon disk	10 µL	35°C	DAD	Agilent Zorbax Eclipse XDB C8 5 µm, 150 mm ×4.6 mm
13	In-house method	N/A	Methanol	Add methanol to the mark, homogenise and equilibrate to room temperature	2 µL	40°C	DAD UV VIS	Phenomenex Kinetex XB-C18 2.6 µm, 100 mm × 4.6 mm
14	Manufacturer's method	N/A	Water:Acetonitrile (20:80 v/v)	Sonicate for 5 minutes. Filter through 0.45 µm nylon disk	10 µL	40°C	DAD	Phenomenex Gemini C18 5 µm, 4.6 mm × 150 mm
15	Manufacturer's method	Di-n-pro-pylftalate 2,7171 mg/mL	Acetone	Transfer a quantity of about 50 mg of a.s. to a volumetric flask, add 10 mL of IS. Ultrasonicate for 5 min. Wait until the temperature is stabilized and fill to mark with acetone. Filter before to inject	1 µL	325°C	FID	DB-5 30 m, 0.32 mm × 0.25 mm
16	In-house method	Methyl Benzoate 1.5 mg/mL	Ethyl acetate	Sonicate for 15 min. Filter through Nylon 0.45 µm disk	1 µL	270 ºC	FID	HP -5 5% Phenyl Methyl Siloxane 30.0 m × 0.32 mm × 0.25 µm
17	In-house method	N/A	Acetonitrile	Weigh, disperse in 10 mL water, dilute in acetonitrile to volume	5 µL	25°C	PhotoDA	Phenomenex Kinetex C18 2.6 µm, 100 mm × 4.6 mm

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APPENDIX A
The announcement letter

ANNOUNCEMENT/INVITATION
ITPT2021

Dear Colleagues,

We herewith cordially invite you to participate in the Italian Proficiency Test on the analysis of PPPs in SE and SL. This exercise is organized by the Italian Laboratory of National Institute of Health – Department of Environment and Health. The ITPT2021 is scheduled to run from 15th January until 30th April 2021.

AIMS
Participation in proficiency tests is part of the QA/QC system of laboratories and provides them with an assessment of their analytical performance as well as a comparison with the performance of other laboratories. The general aim is to help laboratories demonstrate adequate analytical performance and, in case of underperformance, to help them identify sources of errors so that the necessary measures for quality improvement can be taken.

TEST ITEM
Ca. 10 g of PPP test Item will be delivered to each participating lab.

TARGET ANALYTES
The analytes are:

Active Substance	Conc (g/L)	Formulation
Fenhexamid	500	SC
Imazamox	80	SL
Trinexapac-Ethyl	116.4	CS

SHIPMENT AND RECEIPT OF THE TEST ITEM
The shipment of the Test Item is planned to start around 15th January 2021. If any laboratory will be on holiday in the week of the shipment, please inform the organizer to rearrange shipment.
Participants must check the integrity and condition of the materials upon receipt and to report within 48h if they accept the materials or not.

IMPORTANT DATES
- The shipment of the Test Items is planned to start around 15 January 2021.
- Submission of results and method information should be done by 30 April 2021.

PARTICIPATION FEE
The participation is free of charge.

RELEVANT DOCUMENTS
Participants are encouraged to employ the method typically run in their lab for these analytes.

SUPPORT AND CONTACT INFORMATION
For any questions about the ITPT-PPP01, please mail to angela.santilio@iss.it

Best regards,

The ITPT2021 Organizing Team

APPENDIX B
Calendar and list of participants

CALENDAR for the ITPT2021

Activity	Dates
Opening of the ITPT2020	4th November 2020
Confirm the participation	30th November 2020
Shipment of the ITPT-PPP03 Test Item	15th January 2021
Confirmation of Sample Receipt and Acceptance	Within 48 h of receipt
Result Submission	30th January – 30th April 2021
Preliminary Report	May 2021
Final Report	June 2021

LIST OF PARTICIPANTS

Italian participants

Arianna Palchetti	*Laboratorio analisi alimenti e sicurezza dei prodotti – APPA BZ*
Luigi Bazzani	*ARPA Emilia Romagna* *Sede secondaria laboratorio Multisito, sezione di Ferrara*
Leonardo Sabatino	*Ministero delle Politiche Agricole Alimentari e Forestali, Ispettorato centrale della tutela della qualità e repressione frodi dei prodotti agroalimentari - Laboratorio di Catania*
Valentina Picardo	*Istituto Superiore di Sanità, Roma*

European participants

Lajos Sándor Benke	*National Food Chain Safety Office- Hungary*
Florentina Ciotea	*National Phytosanitary Authority - Romania*
Frantisek Csicsay	*ÚKSÚP - Bratislava, Slovakia*
Christoph Czerwenka	*AGES GmbH - Wien, Austria*
Kristina Dürkop	*Federal Office of Consumer Protection and Food Safety, Germany*
Eva Jacobsen	*Danish Technological Institute - Aarhus, Denmark*
Helen Karasali	*Benaki Phytopathological Institute – Athens, Greece*
Olga Nováková	*UKZUZ National Reference Laboratory – Brno, Czech Republic*
Benoit Saclier	*Service Commun des Laboratoires, France*
St. Nikolova Petar Ilchev	*CLCT, Bulgary*
Pierre Hucorne	*Walloon Agricultural Research Centre (CRA-W), Belgium*
Javier Garcìa-Hierro Navas	*Laboratorio Arbitral Agroalimentario, Spain*
Paul Martin-Carr Denis	*Pesticides Formulations Laboratory, DAFM, Ireland*

GLOSSARY

Active Ingredient. An active ingredient (AI) is the ingredient in a pharmaceutical drug or plant-health drug that is biologically active. Some products may contain more than one active ingredient.

Analyte. An analyte, component, or chemical species is a substance or chemical constituent that is of interest in an analytical procedure.

CAS number. A CAS Registry Number, also referred to as CASRN or CAS Number, is a unique numerical identifier assigned by the Chemical Abstracts Service (CAS) to every chemical substance described in the open scientific literature (currently including all substances described from 1957 through the present, plus some substances from the early or mid-1900s) including organic and inorganic compounds, minerals, isotopes, alloys and no structural materials (UVCBs, of unknown, variable composition, or biological origin). The registry maintained by CAS is an authoritative collection of disclosed chemical substance information. It currently identifies more than 141 million unique organic and inorganic substances and 67 million protein and DNA sequences, plus additional information about each substance. It is updated with around 15,000 additional new substances daily.

Chemical formula. A chemical formula is a way that chemists describe a molecule. The formula says what atoms, and how many of each type, are in the molecule. Sometimes the formula shows how the atoms are linked, and sometimes the formula shows how the atoms are arranged in space. The letter shows what chemical element each atom is.[1] The subscript shows the number of each type of atom.

% CV. The coefficient of variation (CV) is defined as the ratio of the standard deviation σ to the mean μ multiplied 100: $CV = (\sigma / \mu) \times 100$.

E isomer. is the IUPAC convention of a molecular configuration, if the two groups of higher priority are on opposite sides of the double bond, the bond is assigned the configuration E (from the German word for “opposite” *entgegen*).

Grand Average. The grand mean or average is the mean of the means of several subsamples, as long as the subsamples have the same number of data points. For example, consider several lots, each containing several items. The items from each lot are sampled for a measure of some variable and the means of the measurements from each lot are computed. The mean of the measures from each lot constitutes the subsample mean. The mean of these subsample means is then the grand mean.

Homogeneity. Homogeneity and heterogeneity are concepts often used in the sciences and statistics relating to the uniformity in a substance or organism. A material or image that is homogeneous is uniform in composition or character (i.e., colour, shape, size, weight, height, distribution, texture, language, income, disease, temperature, radioactivity, architectural design, etc.); one that is heterogeneous is distinctly non uniform in one of these qualities.

Internal Standard. An internal standard in analytical chemistry is a chemical substance that is added in a constant amount to samples, the blank and calibration standards in a chemical analysis. This substance can then be used for calibration by plotting the ratio of the analyte signal to the internal standard signal as a function of the analyte concentration of the standards. This is done to correct

for the loss of analyte during sample preparation or sample inlet. The internal standard is a compound that is very similar, but not identical to the chemical species of interest in the samples, as the effects of sample preparation should, relative to the amount of each species, be the same for the signal from the internal standard as for the signal(s) from the species of interest in the ideal case.

MAD. In statistics, the Median Absolute Deviation (MAD) is a robust measure of the variability of a univariate sample of quantitative data. MAD = median of ($|X_i$ – median (Xi) $|_{i=1,2...n}$).

Median. The median is the value separating the higher half of a data sample, a population, or a probability distribution, from the lower half. For a data set, it may be thought of as the "middle" value. For a continuous probability distribution, the median is the value such that a number is equally likely to fall above or below it. The median is a commonly used measure of the properties of a data set in statistics and probability theory. The basic advantage of the median in describing data compared to the mean (often simply described as the "average") is that it is not skewed so much by extremely large or small values, and so it may give a better idea of a "typical" value. Because of this, the median is of central importance in robust statistics.

Modified z-score. The z-score of an observation is defined as $Zi = (X - \mu) / \sigma$, where X is a sample, μ the sample mean and σ the standard deviation. In other words, data is given in units of how many standard deviations it is from the mean. Although it is common practice to use z-scores to identify possible outliers, this can be misleading in particularly for small sample sizes, so is better to use the modified z-score:

$$Zi = 0.6745 \times {}^{(Xi - median)} / MAD$$

The modified z-scores with an absolute value of greater or lower than 3.5 be labelled as an outlier.

Outlier. An outlier is an observation that appears to deviate markedly from other observations in the sample. Identify potential outliers is important because it may indicate a bad data. For example, the data may have been coded incorrectly or an experiment may not have been run correctly. If it can be determined that an outlying point is in fact erroneous, then the outlying value should be deleted from the analysis (or corrected if possible). If it is not possible to simply delete the outlying observation, the use of robust statistical techniques may be considered.

Reference Method. A reference method is an analytic procedure sufficiently free of random or systemic errors to make it useful for validating proposed new analytic procedures for the same analyte. This method has to be accuracy of a definitive method already certified demonstrated through direct comparison and must use primary reference material (standards, glasses, instruments). An in-house method it means that the method is not certified and made with the laboratory's instruments and techniques. The CIPAC methods is an analytical method make following CIPAC's instructions as the Manufacturer's method is make with the Manufacturer's instructions.

SD. The standard deviation (SD, also represented by the Greek letter sigma σ or the Latin letter s) is a measure that is used to quantify the amount of variation or dispersion of a set of data values. A low standard deviation indicates that the data points tend to be close to the mean of the set, while a high standard deviation indicates that the data points are spread out over a wider range of values.

Stability. The stability is a molecular characteristic of a chemical or compound; is the tendency of a material to resist change or decomposition in its natural environment or when exposed to air, heat, light, pressure or other natural conditions or due to internal reaction.

Z isomer. is the IUPAC convention of a molecular configuration, if the two groups of higher priority are on the same side of the double bond, the bond is assigned the configuration Z (from the German word for "together" *zusammen*).

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