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Research Article

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Multi-class, Multi-residue Analysis of 59 Veterinary Drugs in Livestock Products for Screening and Quantification Using Liquid Chromatography-tandem Mass Spectrometry

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Abstract

BACKGROUND: The objective of this study was to develop a comprehensive and simple method for the simultaneous determination of 59 veterinary drug residues in livestock products for safety management.

METHODS AND RESULTS: For sample preparation, we used a modified liquid extraction method, according to which the sample was extracted with 80% acetonitrile followed by incubation at -20°C for 30 min. After centrifugation, an aliquot of the extract was evaporated to dryness at 40°C and analyzed using liquid chromatography combined with tandem mass spectrometry. The method was validated at three concentration levels for beef, pork, chicken, egg, and milk in accordance with the Codex Alimentarius Commission/Guidelines 71-2009. Quantitative analysis was performed using a matrix-matched calibration. As a results, at least 52 (77.6%) out of 66 compounds showed the proper method validation results in terms of both recovery of the target compound and coefficient of variation required by Codex guidelines in livestock products. The limit of quantitation of the method ranged from 0.2 to 1119.6 ng g-1 for all matrices.

CONCLUSION(S): This method was accurate, effective, and comprehensive for 59 veterinary drugs determination in livestock products, and can be used to investigate veterinary drugs from different chemical families for safety management in livestock products.

Key words: LC-MS/MS, Livestock products, Multi-class analysis, Veterinary drug

Introduction

Veterinary drugs have been widely used in medical and veterinary practice to treat and prevent diseases and enhance growth rate and feed efficiency. Currently, the most commonly used veterinary drugs are β-lactams,

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sulfonamides, macrolides, and quinolones [1-5]. If they are not used correctly, this practice could lead to the presence of veterinary drug residues in foods of animal origin. The possible adverse effects of these drugs on public health include allergic reactions in hypersensitive or sensitized individuals and the development of resistant strains of bacteria following the ingestion of sub-therapeutic doses of antimicrobials [6-12]. With the increase in public attention to food safety, regulation of drugs used in animal food production has been imposed in nearly every country [13, 14]. Analytical methods employed for the determination of veterinary drugs must meet the criteria established under regulatory guidance. To ensure food safety, strict regulations for analytical methods in terms of maximum residue limits (MRL) and minimum required performance limits (MRPL) have been stipulated by national and international agencies, such as the Codex Alimentarius Commission and the European Commission.

In Korea, varying degrees of drug MRLs are imposed on livestock products imported from different countries and these products are not inspected for drug residues outside the established MRLs or residue tolerances. To enhance food safety in Korea, the Ministry of Food and Drug Safety (MFDS) has been preparing to introduce a positive list system (PLS). The PLS program for veterinary drugs will be implemented by 2024 or after. Five major livestock products (beef, pork, chicken, eggs and milk) were first subjected to PLS. In the absence of established MRLs in Korea, Codex standards are used as a default policy; failing this, the lowest MRL set for similar products can be used. However, with the implementation of PLS, a default tolerance of 10 $\mu g\ kg^{-1}$ will be applied to drugs with no established Korean MRLs. Following the full implementation of the new system, residual drug substances without established MRLs or residual tolerances are subject to law enforcement [28]. Accordingly, the development of generic, fast, sensitive, and reliable analytical methods that can monitor unauthorized veterinary drugs is required to ensure successful implementation of PLS.

Methods for selecting classes of veterinary drugs are abundant. Multi-class, multi-residue methods are rare due to many analytical challenges which must be overcome in sample preparation. Challenges include the extraction of drugs with wide polarity ranges and characteristics, high concentrations of protein and fat co-extractives in meat that complicate sample clean-up, and tissue enzymes (released during homogenization) that degrade some analytes during the extraction process. Foods of animal origin, such as muscle, liver, and eggs, are complex matrices that may contain 2-47% fat and 10-30% proteins [14]. Therefore, efficient sample extraction and selective matrix clean-up are usually challenging given the need to achieve the desired recovery of multiple veterinary drug compounds.

The analysis of multi-class, multi-residue veterinary drugs in livestock matrices has been reported in literature over the past few years. Several extraction approaches have been proposed for the analysis of feed stuffs and animal products, such as the quick, easy, cheap, effective, rugged, and safe (QuEChERS) approach [15-18], solid-phase extraction (SPE) [19, 26], pressurized liquid extraction (DVPLE) [20], liquid-liquid extraction (LLE) [21, 25], and matrix solid-phase dispersion [22-24].

Veterinary drug residues in food can be determined by liquid chromatography (LC) coupled with ultraviolet (UV), fluorescence detection (FLD), or mass spectrometry (MS). In recent years, multi-class multi-residue methods have been introduced to further increase monitoring efficiency [29, 33, 34]. Traditional analysis technologies, such as LC-UV [37, 38] and LC-FLD [35, 36], cannot meet the requirements for simultaneous detection of multi-class drugs. LC-tandem mass spectrometry (LC-MS/MS) technologies have enabled the realization of multi-residue methodologies owing to their advantages of sensitivity, selectivity, and low interference. In addition, multi-detection methods for the analysis of veterinary drugs using LC coupled with time-of-flight MS (LC-ToF-MS) have been published [30-32]. One of the main advantages is the possibility of analyzing an unlimited number of analytes in a single run because the detection by ToF-MS is not limited by the dwell time. Nevertheless, it can be applied for screening and quantification purposes, but cannot be used as a confirmatory method because of the requirements of regulatory and always requires confirmation of positive findings using an MS/MS detector [41].

This paper describes the development and validation of a simple and effective quantitative screening method using LC-MS/MS for the simultaneous detection of 66 compounds (59 veterinary drugs and 7 metabolites) in livestock products. The validation procedure followed the codex guidelines CAC/GL 71-2009 [27] to apply the method in routine analysis.

Materials and Methods

Chemicals and reagents

All 66 target compounds were of high-purity grade (>90%), and the majority of them were purchased from Dr. Ehrenstorfer (Augsburg, Germany). LC-MS-grade acetonitrile (ACN), methanol (MeOH), and methylene chloride (MC) were purchased from Merck (Darmstadt, Germany). Formic acid (>99%), dimethyl sulfoxide (DMSO), ethylenediaminetetraacetic acid disodium salt dihydrate ($Na_2EDTA \cdot 2H_2O$), sodium chloride (NaCl), and acetic acid (>99%) were purchased from Sigma-aldrich (St. Louis, MO, USA). Ammonium formate (>98%) was supplied by Alfa Aesar (Ward Hill, MA). Anhydrous magnesium sulfate ($MgSO_4$) from JUNSEI Chemical (Tokyo, Japan) and primary secondary amine (PSA) from Agilent Technologies (CA, USA) were supplied. C18 powder (particle size = 55–105 μm, pore size = 125 Å) was purchased from Waters (Milford, MA, USA). Distilled water (DW) was provided by a Milli-Q water system (Merck-Millipore, Zug, Switzerland). Polytetrafluoroethylene (PTFE), polyvinylidene (PVDF), nylon filter (diameter = 15 mm, pore size = 0.2 μm) were purchased from Teknokroma (Barcelona, Spain).

Standard solutions

Stock solutions of the individual veterinary drugs (standards) were prepared at a concentration of 1000 μg mL^{-1} (calculated as a free base). Most of the analytes were dissolved in MeOH, and some of them were dissolved in ACN, DW, and DMSO. Stock solutions were stored at −20°C in amber polypropylene tubes to avoid photodegradation and adsorption onto the glass. A working solution of the standard mixture was prepared and diluted step-by-step with a standard dilution solution to prepare different concentrations of standard solutions. An extra dilution of the analytes was prepared when a lower-fortification mixture was required.

Sample collection

Livestock samples (beef, pork, chicken, egg, milks) were obtained from local supermarkets in South Korea. Upon arrival at the laboratory, all animal tissue samples (over 500 g) were homogenized using a food blender and samples were placed in plastic bags in a freezer at -20°C till analysis.

Comparison of sample preparation methods

The schemes of Testing method (T1) and testing method (T2) were shown in Fig. 1. 'Testing method 1'

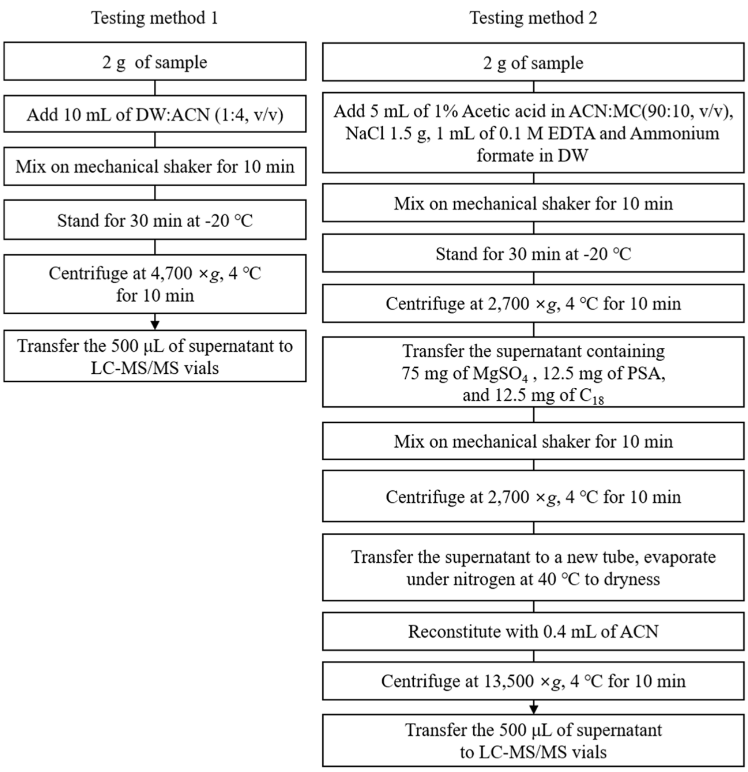

Fig. 1. Schemes of the sample preparation protocol for analysis of veterinary drugs in livestock products.

(T1), cited with minor modification from CLG- MRM 3.02 (FSIS, USDA), was a liquid extraction method with the precipitation under low temperature, and 'testing method 2' (T2), cited with minor modification Y.S, Choi (Dankook Univ., South Korea), was a modified QuEChERS method. EDTA was used in the extraction solution of the T2 method to prevent chelation, even though the target compounds did not appear to form chelates, because the scope of the method could be extended to chelating drugs [42, 43]. NaCl was added to induce phase separation between the aqueous and organic phases; as a result of this salting out effect, analytes in the aqueous phase were driven into the organic phase [42]. Then, the solution was left to stand at -20°C for 30 min to promote the precipitation of lipids and proteins [39].

After that, evaporation and filtration steps were added to improve sensitivity with the testing method (T1). An aliquot of 5 mL of the upper layer (organic phase) was concentrated at 40°C by evaporation with a nitrogen stream to dryness, and the dried samples was reconstituted with 50% ACN followed by filtration through a syringe filter of pore size 0.2 μm. Filtration with PTFE, PVDF, and nylon cartridges were compared to study filtration loss.

Final optimized Sample preparation method

A 2.0-g portion of the livestock samples (beef, pork, chicken, egg, and milks) was weighed into a 50 mL polypropylene centrifuge tube. After the addition of 10 mL 80% ACN (v/v) the samples were shaken for 10 min using a mechanical shaker. The sample tube was then incubated for 30 min at −20°C in a freezer followed by centrifugation at 4,700 ×g at 4°C for 10 min. The supernatant (5 mL) was evaporated to dryness under a stream of nitrogen at 40°C, 50% ACN (1 mL, v/v) was added to the residue. The final extracts were filtered through a 0.2-μm nylon syringe filter, and 5 μL of the filtered sample was injected for LC-MS/MS analysis.

Instrumental conditions

Ultra-high-performance liquid chromatography UHPLC-MS/MS analysis of veterinary drugs and metabolites was performed using a Shimadzu Nexera X2 system (Kyoto, Japan) coupled with a Shimadzu LCMS-8060. Chromatographic separation was achieved on an Xbridge C18 column (Waters, 150 mm × 2.1 mm, particle size = 3.5 μm), the column oven temperature was 40°C and the injection volume was 5 μL. The analytes were eluted with a mobile phase composed of (A) 0.1% formic acid in DW and (B) 0.1% formic acid in ACN at a flow rate of 0.25 mL min^{-1}. The gradient profile was scheduled as follows: initial proportion (98% A and 2% B) for 1 min → linear increase to 70% (B) until 7 min → linear increase to 80% (B) until 7.3 min → linear increase to 98% (B) until 10.2 min → hold 98% (B) until 13.2 min, and then back to 2% (B) until 13.21 min → hold for 2% (B) until 16 min. The mass spectrometric instrument was operated with an electrospray ionization (ESI) interface in positive and negative ion modes. ESI parameters were as follows: positive interface voltage = 4.0 kV, negative interface voltage = -3.0 kV, interface temperature = 350°C, heat block temperature = 300°C, desolvation line (DL) temperature = 150°C, nebulizing gas flow = 3.0 L min^{-1}, and drying gas flow = 10 L min^{-1}. Considering the properties of the screening methods for trace residues, the MS/MS instrument was operated in multiple reactions monitoring (MRM) mode to achieve highly sensitive and selective analysis. MS/MS parameters of the MRM methods were optimized for each compound using automated flow injection analysis of individual standard solutions. Labsolutions (Ver. 5.99) software was used for instrument control and data processing.

Method validation

The performance characteristics of the optimized method were established by a validation procedure according to the Codex guidelines CAC/GL 71-2009. The analytical characteristics evaluated were linearity, accuracy, precision, limit of detection (LOD), and limit of quantitation (LOQ). Targeted testing levels were applied at the MRL level (if they existed) during the validation process. For compounds without MRLs, 10 μg kg^{-1} was used as the target testing level for all five livestock matrices. Linearity was evaluated using matrix-matched calibration with six fortified levels of blank, 0.25×, 0.5×, 1×, 2×, and 4× MRL or 2.5, 5, 10, 20, and 40 μg kg^{-1}, while the blank, 1×, 2×, 5×, 10×, and 20× LOQ for prohibited compounds. Linear regression analysis was performed by plotting the peak area versus the analyte concentrations for compounds with no corresponding internal standard. The accuracy of this method was estimated using recovery studies. The precision of the method was evaluated by performing repeatability and reproducibility experiments. LOD and LOQ were determined as the amounts for which the signal-to-noise ratio (S/N) was higher than 3 and 10, respectively.

Inter-laboratory validation from the two laboratories was conducted to evaluate the ruggedness of the method. Each sample was prepared at the same fortified levels, and analyzed following the same analytical procedure at each of the two participating laboratories, using an individual LC-MS/MS system. Linearity was demonstrated for all compounds by preparing a six-levels matrix-matched calibration curve in the range of target concentrations (blank, 0.25×, 0.5×, 1×, 2×, and 4× MRL or 2.5, 5, 10, 20, and 40 μg kg^{-1}, and blank, 1×, 2×, 5×, 10×, and 20× LOQ). Accuracy and precisions were determined by analyzing blank samples at three different concentration in five replicates for each concentration (0.5×, 1×, 2× MRL or 5, 10, 20 μg kg^{-1}, and 1×, 2×, 10× LOQ). The accuracy and precision of the five replicate measurements per laboratory were expressed as the recovery (%) and coefficient of variation (CV, %).

Results and Discussion

LC–MS/MS analysis

The use of LC for the separation of veterinary drugs for simultaneous determination is particularly useful because veterinary drugs have highly variable chemical structures. Various parameters, such as the initial conditions, holding time, and gradient steps, were optimized for all compounds. All the target analytes were well separated and showed symmetric peaks in the total ion chromatogram, permitting their identification, confirmation, and quantitation. The retention time of the compounds ranged from 1.23 to 13.49 min within a 16-min run time. For quantitation, the characteristic ions of each compound were determined in the multiple reaction monitoring mode of electrospray ionization. Peak identification was achieved by comparing retention times and matching the area ratios of the characteristic ions. The LC-MS/MS parameters for each analyte are listed in Table 1.

Target compounds

To choose the target compounds, a list of candidate veterinary drugs was first made with the help of the MFDS. The candidate list included (1) drugs that established MRL, but were not included in 8.3.1 of the Korean Food Code [32], (2) prohibited drugs in foods by domestic or foreign regulations, and (3) drugs with foreign, but not domestic approval. Several drugs, such as nitrofurans and aminoglycosides, are not included in the candidate list because they are too hydrophilic and require a derivatization step in the sample preparation procedure. Finally, the list of 66 target compounds was completed with the addition of the metabolites of some drugs that should be monitored together.

Optimization of sample preparation

For sample preparation, several generic sample preparation methods were used and then applied to pork, representatively, and recoveries at 100 ng g^{-1} were compared to find a more suitable method for the comprehensive and fast extraction of the 66 target compounds (Fig. 2).

The extraction and clean-up efficiencies were investigated based on the number of compounds, with a recovery criterion of 70-120% with coefficient of variation ≤20%. When using testing method 2 (T2), peaks were not observed for desacetyl cephapirin and desfuroyl ceftiofur in all five livestock matrices. Piperazine was only observed in the eggs. In contrast, acceptable recoveries for all target compounds were obtained using the T1 method. In addition, some high-polarity compounds, such as *N,N*-bis-(4-nitrophenyl) urea, iodo-hydroxyquinoline sulfonic acid, florfenicol amine, 2-hydroxy-4,5-dimethylpyrimidine, and amprolium, were not extracted using the T2 method. In beef and pork, the results for the number of analytes showed similar results with T1 and T2. However, there were significant differences between T1 and T2 in chicken, egg, and milk. Therefore, the T1 method was chosen for sample preparation in this study. The T1 method was beneficial with respect to time because it minimized the sample preparation steps. For different matrices, different types of sorbents, such as NH_4, PSA, and C_{18}, were selected to clean up the interference (pigments, organic acids, sugars, and lipids) from the matrix [18]. C_{18} and PSA were used to effectively remove interfering substances and fat. C_{18} is a hydrocarbon chain that eliminates fats and non-polar interfering substances [14, 40]. PSA is a weak anion exchange sorbent that retains carboxylic acids and fatty acids in samples because it contains two amino groups [44]. However, some methods do not include a clean-up step in the QuEChERS procedure because of the poor recovery of analytes.

Using final optimized sample preparation methods,

Table 1. Optimal MRM parameters for each target compound

No.	Compounds	Molecular formula	Exact mass g/mol	Retention time (min)	Ionization mode	Precursor ion m/z	Product ion m/z (CE, eV)		
1	Gamithromycin	$C_{40}H_{76}N_2O_{12}$	776.5	5.95	Positive	777.3	83.2(23)	116.2(27)	158.2(24)
2	Guaifenesin	$C_{10}H_{14}O_4$	198.1	5.81	Positive	199	163.2(9)	77.2(34)	122.2(21)
3	Narasin	$C_{43}H_{72}O_{11}$	764.5	13.21	Negative	763.2	255.3(36)	221.1(42)	407.3(35)
4	Nitroxoline	$C_9H_6N_2O_3$	190	7.14	Positive	191	127.1(34)	90.1(17)	117.2(29)
5	Naftazone	$C_{11}H_9N_3O_2$	215.1	7.01	Positive	216	115.1(30)	143.1(18)	128.1(27)
6	Nitroxynil	$C_7H_3IN_2O_3$	289.9	7.76	Negative	288.7	162.2(21)	127.0(27)	215.1(24)
7	Decoquinate	$C_{24}H_{35}NO_5$	417.3	10.27	Positive	418.1	204.1(43)	148.1(27)	232.1(34)
8	Dehydrocholic acid	$C_{24}H_{34}O_5$	402.2	7.36	Positive	403.1	385.3(9)	367.3(16)	349.3(18)
9	Dexamethasone	$C_{22}H_{29}FO_5$	392.2	7.1	Negative	437	361.3(21)	325.3(24)	307.2(35)
10	Doramectin	$C_{50}H_{74}O_{14}$	898.5	11.61	Positive	899.1	777.4(45)	449.3(48)	353.3(53)
11	Dichlorvos	$C_4H_7Cl_2O_4P$	220	7.25	Positive	220.9	109.1(17)	79.0(26)	180.1(6)
12	Lubabegron	$C_{29}H_{29}N_3O_3S$	499.2	7.72	Positive	499.9	187.1(35)	250.2(23)	209.1(40)
13	Maduramycin	$C_{47}H_{83}NO_{17}$	933.6	13.49	Positive	934.3	551.4(25)	629.4(27)	393.2(29)
14	Metomidate	$C_{13}H_{14}N_2O_2$	230.1	6.65	Positive	231	105.2(24)	127.1(9)	77.1(51)
15	Methylbenzoquate	$C_{22}H_{23}NO_4$	365.2	8.59	Positive	366	201.2(32)	334.2(22)	145.2(46)
16	Monensin	$C_{36}H_{62}O_{11}$	670.4	12.82	Negative	670.2	638.3(40)	101.1(49)	87.1(52)
17	Buparvaquone	$C_{21}H_{26}O_3$	326.2	11.7	Negative	325	186.2(35)	297.3(30)	158.2(36)
18	Cyromazine	$C_6H_{10}N_6$	166.1	3.69	Positive	167	60.2(11)	68.1(29)	83.2(16)
19	Salinomycin	$C_{42}H_{70}O_{11}$	750.5	12.62	Negative	749.2	241.2(37)	221.3(41)	407.2(36)
20	Cefacetrile	$C_{13}H_{13}N_3O_6S$	339.1	5.19	Positive	361.9	258.1(14)	274.1(14)	302.1(10)
21	Cephaprin	$C_{17}H_{17}N_3O_6S_2$	423.1	4.54	Positive	423.9	152.1(24)	181.1(13)	124.0(43)
21-1	Desactyl cephaprin	$C_{15}H_{15}N_3O_5S_2$	381.1	3.84	Positive	381.9	112.1(22)	152.1(26)	124.2(42)
22	Cefalonium	$C_{20}H_{18}N_4O_5S_2$	458.1	5.13	Positive	458.9	152.1(20)	123.1(14)	185.1(24)
23	Ceftiofur	$C_{19}H_{17}N_5O_7S_3$	523	6.34	Positive	523.8	241.1(18)	125.1(53)	210.1(21)
23-1	Desfuroyl ceftiofur	$C_{14}H_{15}N_5O_5S_3$	429	5.48	Positive	429.7	125.1(29)	227.1(22)	285.1(17)
24	Cymiazole	$C_{12}H_{14}N_2S$	218.1	6.06	Positive	219	171.2(24)	144.2(28)	77.1(55)
25	Aminopyrine	$C_{13}H_{17}N_3O$	231.1	4.63	Positive	232.1	98.2(21)	111.2(16)	56.1(37)
26	Amitraz	$C_{19}H_{23}N_3$	293.2	10.41	Positive	294.1	163.2(15)	117.1(41)	107.2(42)
26-1	2,4-Dimethylaniline	$C_8H_{11}N$	121.1	5.07	Positive	122	107.2(20)	79.1(15)	51.1(20)
27	Abamectin	$C_{48}H_{72}O_{14}$	872.5	11.12	Positive	895.3	751.4(52)	327.3(43)	449.3(48)
28	Acrinol	$C_{18}H_{21}N_3O_4$	343.2	6.01	Positive	344	197.2(30)	196.1(43)	225.2(23)
29	Anthranilic acid	$C_7H_7NO_2$	137.1	5.92	Positive	138.1	120.2(13)	65.1 (27)	92.1(21)
30	Amprolium	$C_{14}H_{19}ClN_4$	278.1	1.58	Positive	243.1	150.2(11)	122.2(23)	94.2(19)
31	Ethoxyquin	$C_{14}H_{19}NO$	217.2	7.85	Positive	218.1	160.2(32)	148.2(22)	174.2(25)
31-1	Ethoxyquin dimer	$C_{28}H_{36}N_2O_2$	432.3	12.58	Positive	433.1	216.2(25)	375.3(32)	188.1(39)
32	Eprinomectin	$C_{50}H_{75}NO_{14}$	913.5	10.52	Positive	914.2	186.2(23)	154.3(35)	144.1(43)
33	Iodo hydroxy quinoline sulfonic acid	$C_9H_6INO_4S$	350.9	5.18	Negative	350	159.2(30)	223.1(26)	127.0(30)
34	Ivermectin	$C_{48}H_{74}O_{14}$	874.5	12.47	Positive	897.2	753.4(40)	329.3(54)	609.3(49)
35	β-Zeranol	$C_{18}H_{26}O_5$	322.2	7.37	Negative	321.1	277.3(24)	303.2(24)	275.2(26)
36	α-Zeranol	$C_{18}H_{26}O_5$	322.2	7.7	Negative	321.2	277.3(24)	303.2(23)	259.3(27)
37	Zoalene	$C_8H_7N_3O_5$	225	6.28	Negative	224.1	181.1(11)	77.1(26)	42.1(14)
37-1	3-Amino-5-nitro-o-toluamide (3-ANOT)	$C_8H_9N_3O_3$	195.1	4.68	Positive	196	107.2(19)	77.3(40)	106.2(24)

No.	Compounds	Molecular formula	Exact mass g/mol	Retention time (min)	Ionization mode	Precursor ion m/z	Product ion m/z (CE, eV)		
38	Medroxyprogesterone acetate	$C_{24}H_{34}O_4$	386.3	9.32	Positive	387.1	327.3(14)	123.1(27)	285.3(19)
39	Melengestrol acetate	$C_{25}H_{32}O_4$	396.2	9.31	Positive	397	279.2(21)	221.2(41)	236.2(30)
40	Trenbolone acetate	$C_{18}H_{22}O_2$	270.2	7.41	Positive	271.1	253.3(20)	199.2(24)	128.1(55)
41	Clanobutin	$C_{18}H_{18}ClNO_4$	347.1	7.93	Positive	347.9	111.1(47)	139.1(18)	192.1(15)
42	Chlorpyrifos	$C_9H_{11}Cl_3NO_3PS$	348.9	10.54	Positive	349.8	97.0(29)	198.0(18)	125.1(19)
43	Tolfenamic acid	$C_{14}H_{12}ClNO_2$	261.1	9.52	Positive	262	244.2(14)	180.2(41)	209.2(27)
44	Triamcinolone	$C_{21}H_{27}FO_6$	394.2	6.09	Positive	394.9	225.1(20)	357.2(13)	339.2(13)
45	Thiophanate	$C_{14}H_{18}N_4O_4S_2$	370.1	8.06	Positive	370.8	151.1(20)	352.2(12)	93.2(53)
46	Tylvalosin	$C_{53}H_{87}NO_{19}$	1041.6	7.87	Positive	1042.2	109.0(45)	174.1(38)	229.1(40)
46-1	Tylosin-3-acetate (3-AT)	$C_{48}H_{79}NO_{18}$	957.5	7.03	Positive	958.2	174.1(38)	109.0(47)	772.4(31)
47	Phenothiazine	$C_{12}H_9NS$	199.1	9.27	Positive	200.1	168.2(22)	166.2(36)	140.2(50)
48	Pheylbutazone	$C_{19}H_{20}N_2O_2$	308.2	9.14	Positive	309	120.2(19)	77.1(50)	92.1(31)
49	Pentamethylene tetrazol	$C_6H_{10}N_4$	138.1	5.34	Positive	139	55.2(26)	69.2(20)	41.1(30)
50	Phosmet	$C_{11}H_{12}NO_4PS_2$	317	8.58	Positive	317.8	160.1(19)	105.2(42)	133.1(33)
51	Phoxim	$C_{12}H_{15}N_2O_3PS$	298.1	9.72	Positive	299	129.1(12)	153.1(8)	97.0(20)
52	Fumagillin	$C_{38}H_{57}NO_7$	458.2	9.02	Positive	459.2	131.2(28)	177.2(16)	233.3(15)
53	Prednisolone	$C_{21}H_{28}O_5$	360.2	6.6	Positive	361	147.2(21)	171.2(26)	343.3(10)
54	Florfenicol	$C_{12}H_{14}Cl_2FNO_4S$	357	6.31	Negative	356	185.2(20)	336.1(12)	219.2(13)
54-1	Florfenicol amine	$C_{10}H_{14}FNO_3S$	247.1	3.2	Positive	248	230.2(14)	130.1(26)	91.1(49)
55	Fluralaner	$C_{22}H_{17}Cl_2F_6N_3O_3$	555.1	9.69	Positive	555.8	400.1(21)	160.0(43)	132.2(54)
56	Flumethasone	$C_{22}H_{28}F_2O_5$	410.2	7.14	Positive	411.4	253.2(16)	77.3(10)	371.2(10)
57	Fluvalinate	$C_{26}H_{22}ClF_3N_2O_3$	502.1	11.37	Positive	502.9	181.2(27)	208.2(13)	152.1(55)
58	Piperazine	$C_4H_{10}N_2$	86.1	1.23	Positive	87	44.2(20)	70.3(9)	46.1(17)
59	2-Hydroxy-4,6-dimethylpyrimidine	$C_6H_8N_2O$	124.1	1.57	Positive	125	82.1(21)	107.2(20)	67.1 (24)

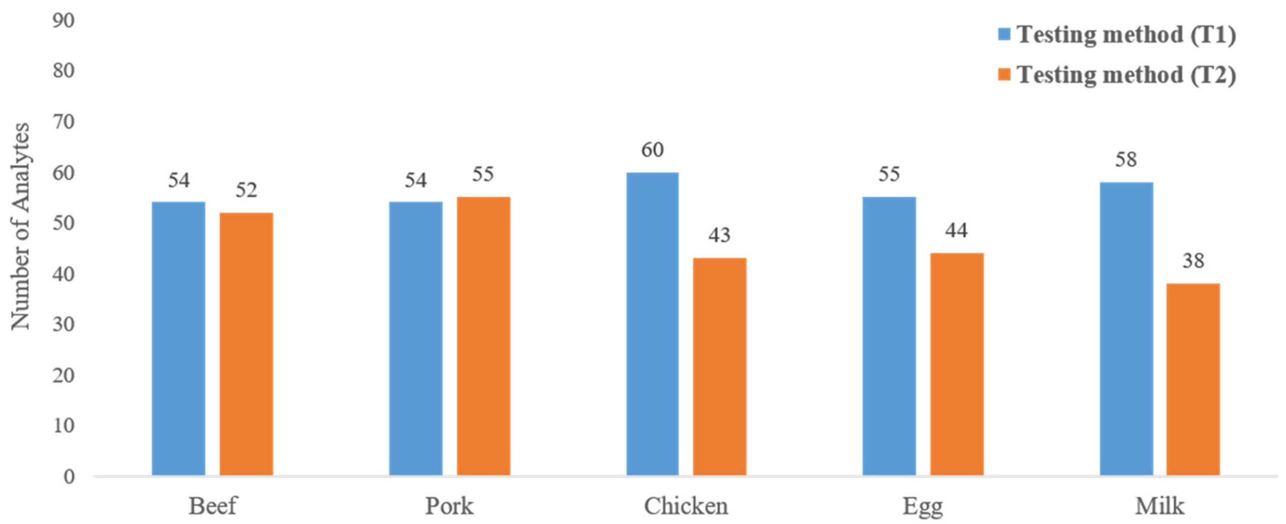

Fig. 2. Number of veterinary drugs satisfying the recovery rates of 70-120% and CV≤20% using the testing method 1 and 2.

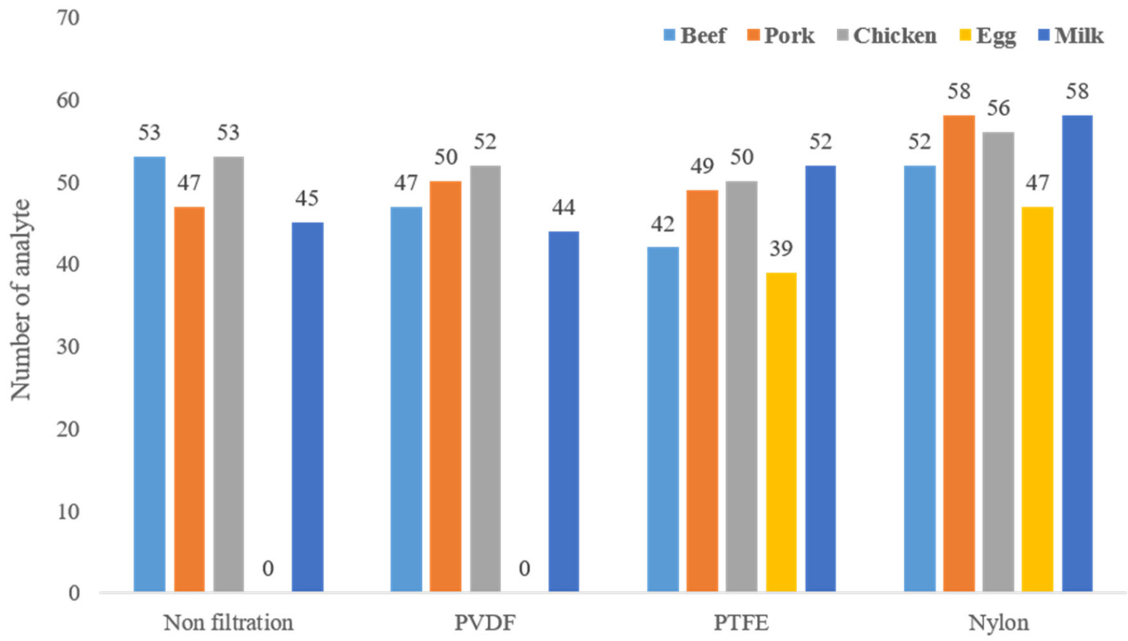

Fig. 3. Number of veterinary drugs satisfying the recovery rates and CV of Codex guidelines by filtration types.

Table 2. Inter-laboratory validation results of analytical method for beef, pork, and chicken.

No.	Compounds	Beef				Pork				Chicken			
		Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5		
			Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.
1	Gamithromycin	10	110 (6)	86 (12)	98 (14)	50	119 (10)	113 (2)	116 (20)	5	92 (13)	102 (13)	97 (15)
		20	100 (5)	88 (12)	94 (10)	100	89 (10)	105 (5)	97 (14)	10	105 (8)	103 (14)	104 (12)
		40	101 (4)	101 (11)	101 (9)	200	72 (10)	100 (4)	86 (19)	20	118 (9)	103 (7)	111 (16)
2	Guaifenesin	5	105 (11)	84 (10)	95 (15)	5	87 (27)	107 (12)	97 (19)	5	111 (22)	94 (10)	103 (18)
		10	112 (11)	93 (6)	103 (13)	10	94 (11)	84 (9)	89 (10)	10	112 (26)	100 (12)	106 (18)
		20	107 (8)	117 (2)	112 (7)	20	98 (5)	78 (7)	88 (12)	20	98 (10)	100 (13)	99 (9)
3	Narasin	5	95 (9)	98 (9)	97 (10)	5	92 (8)	112 (5)	102 (12)	50	93 (8)	112 (5)	103 (11)
		10	101 (9)	98 (16)	100 (10)	10	92 (5)	86 (7)	89 (6)	100	99 (12)	95 (3)	97 (9)
		20	99 (5)	93 (10)	96 (11)	20	93 (5)	79 (9)	86 (9)	200	97 (13)	83 (3)	90 (12)
4	Nitroxoline	5	90 (12)	112 (3)	101 (14)	5	105 (18)	105 (6)	105 (13)	5	81 (7)	80 (8)	81 (6)
		10	93 (6)	90 (4)	92 (5)	10	85 (11)	80 (7)	83 (9)	10	93 (6)	107 (5)	100 (6)
		20	87 (7)	91 (3)	89 (6)	20	80 (1)	84 (2)	82 (3)	20	104 (6)	108 (5)	106 (4)
5	Naftazone	5	108 (9)	90 (13)	99 (15)	5	109 (12)	103 (5)	106 (10)	5	97 (7)	98 (16)	98 (12)
		10	98 (5)	91 (12)	95 (8)	10	102 (9)	81 (13)	92 (13)	10	94 (6)	92 (14)	93 (9)
		20	106 (4)	97 (11)	102 (11)	20	98 (3)	72 (3)	85 (15)	20	95 (9)	104 (3)	100 (7)
6	Nitroxynil	200	110 (4)	-	-	5	81 (9)	115 (3)	98 (18)	5	77 (19)	76 (3)	77 (17)
		400	119 (6)	-	-	10	85 (13)	98 (9)	92 (13)	10	113 (8)	99 (11)	106 (10)
		800	114 (6)	-	-	20	103 (3)	78 (1)	91 (13)	20	118 (9)	107 (12)	113 (10)
7	Decoquinate	5	117 (12)	112 (17)	115 (22)	500	116 (11)	96 (3)	106 (11)	500	109 (7)	-	-
		10	109 (15)	111 (7)	110 (13)	1000	95 (5)	78 (6)	87 (10)	1000	90 (4)	-	-
		20	102 (4)	110 (9)	106 (8)	2000	93 (5)	73 (2)	83 (12)	2000	64 (4)	-	-
8	Dehydrocholic acid	5	106 (18)	96 (11)	101 (12)	5	98 (16)	119 (6)	109 (14)	5	115 (18)	100 (6)	108 (13)
		10	89 (26)	93 (9)	91 (15)	10	73 (22)	88 (6)	81 (18)	10	113 (9)	109 (8)	111 (9)
		20	105 (12)	91 (5)	98 (10)	20	101 (20)	81 (6)	91 (19)	20	104 (12)	104 (7)	104 (9)

No.	Compounds	Beef				Pork				Chicken			
		Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5		
			Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.
9	Dexamethasone	0.5	102 (7)	90 (11)	96 (10)	0.5	97 (7)	98 (7)	98 (13)	0.5	88 (6)	112 (17)	100 (20)
		1	107 (10)	90 (26)	99 (17)	1	111 (8)	83 (6)	97 (14)	1	114 (14)	91 (19)	103 (17)
		2	109 (5)	105 (12)	107 (8)	2	108 (5)	73 (6)	91 (21)	2	107 (9)	91 (9)	99 (13)
10	Doramectin	5	93 (18)	91 (12)	92 (15)	3	108 (19)	82 (8)	95 (18)	5	83 (11)	81 (11)	82 (10)
		10	110 (27)	91 (19)	101 (24)	5	107 (10)	75 (6)	91 (21)	10	100 (7)	78 (14)	89 (16)
		20	110 (18)	84 (13)	97 (21)	10	96 (11)	72 (2)	84 (16)	20	102 (7)	76 (11)	89 (18)
11	Dichlorvos	25	118 (6)	79 (3)	99 (22)	25	-	-	-	25	105 (10)	-	-
		50	116 (16)	120 (1)	118 (10)	50	-	-	-	50	105 (12)	-	-
		100	101 (15)	106 (2)	104 (10)	100	-	-	-	100	91 (17)	-	-
12	Lubabegron	1	119 (3)	88 (14)	104 (15)	5	110 (7)	113 (2)	112 (5)	5	99 (7)	95 (3)	97 (6)
		2	107 (5)	92 (14)	100 (10)	10	102 (7)	88 (9)	95 (9)	10	105 (7)	106 (7)	106 (6)
		4	106 (4)	95 (10)	101 (10)	20	93 (6)	71 (1)	82 (13)	20	108 (7)	100 (6)	104 (6)
13	Maduramycin	5	119 (3)	86 (7)	103 (18)	5	112 (8)	111 (4)	112 (6)	50	104 (11)	95 (5)	100 (10)
		10	103 (4)	92 (18)	98 (13)	10	107 (5)	89 (9)	98 (12)	100	115 (18)	100 (2)	108 (13)
		20	113 (6)	93 (15)	103 (15)	20	112 (3)	75 (3)	94 (21)	200	114 (7)	100 (3)	107 (9)
14	Methomidate	5	110 (8)	98 (10)	104 (11)	5	92 (2)	87 (2)	90 (15)	5	102 (9)	100 (5)	101 (11)
		10	100 (6)	98 (16)	99 (9)	10	78 (9)	75 (4)	77 (9)	10	89 (3)	104 (8)	97 (8)
		20	96 (9)	96 (8)	96 (10)	20	86 (8)	77 (4)	82 (8)	20	92 (12)	93 (8)	93 (10)
15	Methyl benzoquate	5	115 (1)	96 (16)	106 (16)	5	72 (15)	106 (3)	89 (22)	5	96 (5)	101 (4)	99 (7)
		10	106 (5)	97 (18)	102 (11)	10	95 (10)	79 (5)	87 (10)	10	105 (8)	100 (5)	103 (7)
		20	108 (2)	90 (13)	99 (12)	20	106 (10)	72 (3)	89 (17)	20	102 (10)	99 (4)	101 (6)
16	Monensin	25	103 (9)	96 (20)	100 (14)	25	83 (10)	106 (10)	95 (14)	25	99 (6)	96 (11)	98 (10)
		50	103 (12)	90 (18)	97 (13)	50	94 (10)	91 (6)	93 (7)	50	102 (3)	103 (3)	103 (11)
		100	106 (5)	82 (11)	94 (14)	100	98 (4)	74 (8)	86 (15)	100	100 (2)	98 (3)	99 (7)
17	Buparvaquone	5	105 (5)	103 (14)	104 (10)	5	99 (12)	118 (1)	109 (12)	5	97 (8)	90 (7)	94 (8)
		10	104 (8)	101 (17)	103 (13)	10	102 (6)	84 (11)	93 (13)	10	106 (9)	107 (6)	107 (7)
		20	96 (6)	85 (20)	91 (15)	20	86 (3)	72 (2)	79 (10)	20	99 (2)	109 (10)	104 (7)
18	Cyromazine	5	104 (16)	89 (6)	97 (12)	5	99 (14)	87 (4)	93 (13)	25	93 (7)	104 (3)	99 (8)
		10	114 (8)	92 (13)	103 (12)	10	85 (7)	118 (1)	102 (18)	50	99 (15)	107 (1)	103 (10)
		20	114 (13)	101 (8)	108 (12)	20	77 (9)	118 (3)	98 (22)	100	92 (7)	109 (1)	101 (11)
19	Salinomycin	10	105 (10)	89 (15)	97 (15)	50	116 (6)	88 (2)	102 (15)	50	95 (7)	90 (7)	93 (11)
		20	106 (9)	91 (16)	99 (14)	100	104 (5)	72 (2)	88 (17)	100	96 (5)	86 (4)	91 (14)
		40	106 (2)	93 (4)	100 (7)	200	97 (2)	78 (5)	88 (10)	200	98 (2)	78 (4)	88 (13)
20	Cefacetrile	15	102 (9)	-	-	5	95 (14)	-	-	5	91 (14)	-	-
		30	95 (11)	-	-	10	78 (10)	-	-	10	85 (3)	-	-
		60	112 (7)	-	-	20	75 (2)	-	-	20	80 (14)	-	-
21	Cephapirin	25	118 (6)	98 (9)	108 (10)	5	94 (2)	104 (5)	99 (7)	5	72 (13)	93 (19)	83 (21)
		50	105 (9)	104 (7)	105 (9)	10	78 (11)	115 (4)	97 (21)	10	67 (12)	90 (15)	79 (20)
		100	108 (2)	99 (8)	104 (9)	20	72 (2)	117 (7)	95 (26)	20	79 (10)	98 (7)	89 (14)
21-1	Desacetyl cephapirin	25	119 (9)	75 (11)	97 (21)	5	110 (10)	53 (45)	82 (43)	5	100 (12)	100 (51)	100 (30)
		50	110 (9)	92 (11)	101 (11)	10	101 (19)	40 (83)	71 (59)	10	82 (9)	100 (30)	91 (24)
		100	111 (15)	99 (11)	105 (22)	20	72 (2)	90 (21)	81 (52)	20	99 (5)	102 (15)	101 (23)
22	Cefalonium	5	93 (20)	80 (12)	87 (16)	5	107 (17)	97 (15)	102 (15)	5	109 (22)	97 (6)	103 (17)
		10	95 (15)	82 (12)	89 (13)	10	90 (22)	77 (10)	84 (23)	10	107 (12)	98 (20)	103 (16)
		20	102 (6)	103 (15)	103 (13)	20	104 (10)	100 (6)	102 (8)	20	118 (7)	101 (5)	110 (10)

No.	Compounds	Beef				Pork				Chicken			
		Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5		
			Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.
23	Ceftiofur	500	86 (6)	85 (13)	86 (8)	500	91 (8)	119 (1)	105 (15)	5	98 (16)	104 (11)	101 (11)
		1000	91 (2)	91 (15)	91 (12)	1000	88 (4)	89 (7)	89 (5)	10	103 (12)	96 (6)	100 (8)
		2000	105 (7)	102 (8)	104 (6)	2000	103 (5)	73 (2)	88 (18)	20	107 (3)	103 (7)	105 (6)
23-1	Desfuroyl ceftiofur	500	86 (9)	84 (4)	85 (7)	500	108 (11)	115 (1)	112 (8)	5	-	-	-
		1000	90 (10)	105 (3)	98 (11)	1000	87 (17)	86 (1)	87 (11)	10	-	-	-
		2000	92 (4)	94 (4)	93 (4)	2000	109 (4)	78(4)	94 (18)	20	-	-	-
24	Cymiazole	5	113 (16)	111 (7)	112 (14)	5	86 (8)	108 (2)	97 (15)	5	113 (10)	100 (6)	107 (10)
		10	90 (9)	103 (8)	97 (9)	10	72 (17)	78 (5)	75 (10)	10	96 (14)	99 (6)	98 (10)
		20	94 (10)	99 (14)	97 (12)	20	84 (9)	72 (2)	78 (8)	20	88 (10)	82 (5)	85 (9)
25	Aminopyrine	5	78 (5)	87 (9)	83 (9)	5	86 (35)	93 (2)	90 (23)	5	105 (16)	94 (11)	100 (12)
		10	80 (18)	94 (9)	87 (15)	10	61 (23)	79 (5)	70 (19)	10	88 (24)	98 (16)	93 (16)
		20	84 (17)	104 (6)	94 (17)	20	78 (33)	74 (1)	76 (22)	20	106 (18)	93 (2)	100 (11)
26	Amitraz	25	-	-	-	25	104 (22)	228 (3)	166 (40)	5	88 (21)	108 (7)	98 (17)
		50	-	-	-	50	69 (12)	169 (11)	119 (46)	10	101 (19)	97 (20)	99 (19)
		100	-	-	-	100	63 (12)	350 (5)	207 (74)	20	104 (7)	85 (35)	95 (24)
26-1	2,4-dimethylaniline	25	97 (17)	83 (1)	90 (14)	25	108 (8)	118 (7)	113 (8)	5	107 (11)	128 (10)	118 (13)
		50	83 (18)	102 (2)	93 (16)	50	96 (9)	98 (3)	97 (7)	10	108 (7)	94 (7)	101 (10)
		100	81 (4)	118 (2)	100 (19)	100	109 (3)	101 (2)	105 (5)	20	100 (6)	84 (3)	92 (10)
27	Abamectin	5	95 (16)	96 (21)	96 (15)	5	93 (29)	86 (4)	90 (18)	5	107 (12)	100 (13)	104 (63)
		10	74 (28)	97 (12)	86 (21)	10	94 (13)	75 (6)	85 (14)	10	96 (18)	102 (8)	99 (24)
		20	84 (18)	102 (11)	93 (17)	20	95 (17)	73 (1)	84 (18)	20	76 (14)	103 (10)	90 (22)
28	Acrinol	5	113 (5)	111 (12)	112 (15)	5	105 (10)	112 (5)	109 (10)	5	106 (7)	103 (10)	105 (12)
		10	99 (5)	107 (16)	103 (11)	10	110 (4)	85 (7)	98 (12)	10	114 (11)	102 (5)	108 (13)
		20	101 (7)	110 (15)	106 (10)	20	102 (6)	75 (2)	89 (18)	20	108 (4)	92 (8)	100 (14)
29	Anthralic acid	5	120 (6)	109 (5)	115 (10)	5	101 (14)	112 (5)	107 (10)	5	83 (11)	100 (8)	92 (13)
		10	101 (6)	107 (9)	104 (8)	10	89 (6)	85 (7)	87 (7)	10	97 (10)	100 (9)	99 (9)
		20	104 (4)	112 (6)	108 (6)	20	96 (7)	75 (2)	86 (13)	20	97 (12)	97 (5)	97 (8)
30	Ampurolium	250	83 (8)	89 (6)	86 (8)	5	119 (3)	118 (3)	119 (3)	250	96 (8)	-	-
		500	91 (10)	91 (17)	91 (13)	10	103 (9)	92 (5)	98 (8)	500	101 (7)	-	-
		1000	104 (5)	104 (9)	104 (7)	20	108 (6)	72 (1)	90 (24)	1000	103 (6)	-	-
31	Ethoxyquin	5	109 (12)	-	-	5	114 (6)	111 (8)	113 (7)	5	98 (14)	103 (15)	101 (13)
		10	93 (10)	-	-	10	84 (9)	93 (8)	89 (9)	10	100 (13)	103 (6)	102 (11)
		20	86 (13)	-	-	20	79 (5)	96 (17)	88 (17)	20	99 (14)	93 (10)	96 (11)
31-1	Ethoxyquin dimer	5	117 (4)	91 (19)	104 (19)	5	115 (14)	115 (3)	115 (3)	5	92 (11)	94 (4)	93 (10)
		10	110 (18)	89 (15)	100 (20)	10	75 (9)	89 (3)	82 (3)	10	99 (10)	102 (2)	101 (6)
		20	92 (12)	81 (17)	87 (21)	20	116 (2)	71 (1)	94 (1)	20	97 (7)	107 (3)	102 (6)
32	Eprinomectin	50	119 (9)	97 (12)	108 (20)	5	102 (19)	106 (10)	104 (15)	5	94 (22)	-	-
		100	102 (8)	100 (19)	101 (15)	10	108 (15)	81 (7)	95 (19)	10	88 (15)	-	-
		200	112 (8)	108 (14)	110 (9)	20	89 (11)	85 (4)	87 (9)	20	111 (13)	-	-
33	Iodo hydroxy quinoline sulfonic acid	5	101 (14)	108 (20)	105 (16)	5	90 (10)	118 (6)	104 (16)	5	119 (6)	98 (13)	109 (13)
		10	99 (13)	85 (10)	92 (13)	10	80 (16)	102 (11)	91 (18)	10	87 (24)	95 (12)	91 (19)
		20	104 (13)	85 (7)	95 (13)	20	76 (6)	103 (12)	90 (19)	20	77 (18)	89 (10)	83 (19)
34	Ivermectin	15	114 (18)	96 (13)	105 (18)	5	117 (24)	101 (4)	109 (18)	5	99 (8)	91 (5)	95 (13)
		30	85 (17)	101 (12)	93 (16)	10	112 (23)	81 (7)	97 (23)	10	86 (19)	98 (6)	92 (18)
		60	97 (12)	94 (10)	96 (10)	20	119 (10)	75 (4)	97 (27)	20	107 (16)	110 (3)	109 (13)

No.	Compounds	Beef Fortification (ng g^{-1})	Beef Recovery (CV), n=5 Lab. A	Lab. B	Inter-Lab.	Pork Fortification (ng g^{-1})	Pork Recovery (CV), n=5 Lab. A	Lab. B	Inter-Lab.	Chicken Fortification (ng g^{-1})	Chicken Recovery (CV), n=5 Lab. A	Lab. B	Inter-Lab.
35	β-Zeranol	1	91 (53)	115 (2)	103 (7)	5	108 (9)	101 (5)	105 (8)	5	98 (13)	96 (14)	97 (10)
		2	114 (19)	93 (14)	104 (15)	10	99 (4)	79 (7)	89 (11)	10	109 (9)	100 (10)	105 (9)
		4	112 (15)	94 (11)	103 (12)	20	102 (11)	84 (5)	93 (15)	20	94 (6)	94 (15)	94 (11)
36	α-Zeranol	1	108 (25)	94 (20)	101 (22)	5	99 (8)	103 (5)	101 (7)	5	85 (9)	95 (8)	90 (10)
		2	117 (19)	98 (6)	108 (15)	10	105 (5)	84 (10)	95 (13)	10	102 (10)	97 (20)	100 (12)
		4	111 (12)	99 (10)	105 (11)	20	108 (3)	73 (3)	91 (21)	20	98 (12)	99 (7)	99 (9)
37	Zoalene	5	92 (13)	96 (13)	94 (13)	5	112 (19)	108 (7)	110 (13)	1500	101 (8)	106 (4)	104 (8)
		10	85 (6)	105 (10)	95 (14)	10	116 (13)	82 (5)	99 (21)	3000	103 (3)	114 (3)	109 (7)
		20	103 (12)	111 (3)	107 (9)	20	117 (9)	88 (9)	103 (17)	6000	109 (5)	104 (7)	107 (5)
37-1	3-ANOT	5	96 (21)	77 (20)	87 (20)	5	112 (6)	106 (5)	109 (5)	1500	94 (10)	91 (2)	93 (21)
		10	99 (5)	88 (22)	94 (13)	10	93 (3)	83 (12)	88 (9)	3000	107 (5)	105 (7)	106 (12)
		20	103 (3)	103 (10)	103 (9)	20	100 (4)	75 (1)	88 (17)	6000	103 (2)	113 (1)	108 (10)
38	Medroxy progesterone acetate	2	81 (8)	88 (11)	85 (9)	2	120 (7)	106 (7)	113 (8)	2	120 (14)	89 (3)	105 (19)
		4	84 (8)	92 (6)	88 (7)	4	104 (4)	90 (12)	97 (11)	4	98 (10)	95 (9)	97 (8)
		20	92 (3)	99 (7)	96 (5)	20	96 (4)	114 (4)	105 (10)	20	98 (9)	91 (5)	95 (7)
39	Melengestrol acetate	0.5	72 (13)	86 (14)	79 (16)	5	106 (7)	110 (3)	108 (5)	5	91 (12)	91 (21)	91 (16)
		1	93 (17)	79 (20)	86 (20)	10	105 (4)	82 (14)	94 (15)	10	95 (9)	92 (14)	94 (10)
		2	97 (11)	99 (15)	98 (13)	20	102 (5)	75 (2)	89 (17)	20	99 (7)	104 (11)	102 (8)
40	Trenbolone acetate	1	113 (10)	100 (12)	107 (11)	5	112 (9)	114 (4)	113 (6)	5	115 (11)	99 (9)	107 (15)
		2	114 (5)	103 (11)	109 (10)	10	101 (7)	76 (6)	89 (13)	10	103 (4)	102 (5)	103 (5)
		4	103 (5)	100 (13)	102 (10)	20	99 (2)	74 (2)	87 (13)	20	98 (6)	96 (6)	97 (8)
41	Clanobutin	5	114 (7)	87 (10)	101 (15)	5	96 (11)	94 (2)	95 (12)	5	106 (8)	95 (3)	101 (9)
		10	98 (6)	91 (7)	95 (8)	10	99 (4)	77 (4)	88 (12)	10	101 (7)	103 (4)	102 (5)
		20	96 (5)	95 (6)	96 (8)	20	89 (5)	73 (3)	81 (10)	20	99 (7)	100 (5)	100 (5)
42	Chlorpyrifos	500	101 (14)	-	-	10	96 (12)	118 (1)	107 (12)	5	120 (10)	89 (12)	105 (19)
		1000	104 (13)	-	-	20	88 (8)	73 (5)	81 (10)	10	96 (9)	103 (4)	100 (8)
		2000	79 (9)	-	-	40	83 (4)	74 (2)	79 (7)	20	86 (12)	86 (20)	86 (16)
43	Tolfenamic acid	25	120 (8)	98 (15)	109 (16)	25	105 (9)	98 (3)	102 (7)	5	96 (18)	93 (3)	95 (12)
		50	110 (10)	97 (15)	104 (12)	50	94 (9)	73 (8)	84 (16)	10	90 (15)	99 (3)	95 (11)
		100	95 (4)	107 (10)	101 (12)	100	81 (4)	72 (3)	77 (7)	20	105 (17)	98 (7)	102 (12)
44	Triamcinolone	5	119 (17)	97 (11)	108 (15)	5	115 (20)	102 (6)	109 (13)	5	98 (13)	94 (10)	96 (11)
		10	98 (10)	97 (13)	98 (9)	10	103 (12)	79 (5)	91 (15)	10	98 (14)	100 (2)	99 (9)
		20	106 (6)	101 (10)	104 (9)	20	101 (9)	74 (4)	88 (14)	20	103 (7)	106 (5)	105 (6)
45	Thiophanate	5	119 (8)	95 (12)	107 (14)	5	96 (9)	105 (3)	101 (8)	5	98 (8)	106 (2)	102 (5)
		10	110 (8)	99 (16)	105 (11)	10	88 (3)	81 (6)	85 (9)	10	96 (1)	102 (4)	99 (4)
		20	106 (5)	102 (16)	104 (10)	20	87 (0)	73 (2)	80 (13)	20	96 (9)	98 (2)	97 (6)
46	Tylvalosin	5	93 (24)	109 (7)	101 (15)	25	118 (14)	103 (4)	111 (11)	13	117 (13)	106 (12)	112 (13)
		10	90 (21)	106 (16)	98 (15)	50	107 (13)	72 (2)	90 (20)	25	112 (10)	109 (9)	111 (13)
		20	105 (13)	100 (15)	103 (11)	100	115 (16)	78 (3)	97 (20)	50	79 (16)	100 (8)	90 (17)
46-1	3-AT	5	91 (14)	107 (11)	99 (12)	25	88 (10)	110 (7)	99 (14)	13	88 (17)	91 (15)	90 (15)
		10	94 (22)	106 (20)	100 (17)	50	78 (19)	77 (7)	78 (19)	25	110 (13)	87 (7)	99 (17)
		20	99 (15)	109 (10)	104 (11)	100	97 (12)	95 (4)	96 (9)	50	103 (11)	97 (7)	100 (9)
47	Phenothiazine	5	108 (17)	-	-	5	95 (12)	118 (2)	107 (14)	5	98 (11)	96 (2)	97 (7)
		10	107 (10)	-	-	10	82 (9)	103 (7)	93 (14)	10	83 (8)	102 (3)	93 (11)
		20	118 (15)	-	-	20	83 (2)	113 (3)	98 (17)	20	79 (16)	94 (4)	87 (14)

No.	Compounds	Beef				Pork				Chicken			
		Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5		
			Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.
48	Phenylbutazone	10	87 (16)	108 (7)	98 (14)	10	87 (10)	103 (2)	95 (11)	5	92 (7)	118 (1)	105 (14)
		20	85 (21)	108 (14)	97 (18)	20	80 (5)	83 (7)	82 (6)	10	97 (3)	89 (2)	93 (5)
		100	71 (17)	104 (9)	88 (21)	100	91 (13)	110 (2)	101 (13)	50	96 (5)	107 (1)	102 (6)
49	Pentamethylene tetrazol	5	108 (10)	102 (4)	105 (8)	5	103 (3)	104 (5)	104 (4)	5	115 (14)	96 (9)	106 (13)
		10	95 (23)	93 (14)	94 (18)	10	77 (3)	85 (2)	81 (7)	10	119 (10)	96 (9)	108 (13)
		20	92 (13)	109 (9)	101 (14)	20	73 (3)	102 (1)	88 (16)	20	119 (10)	94 (4)	107 (13)
50	Phosmet	500	99 (14)	107 (3)	103 (10)	5	87 (12)	111 (5)	99 (15)	5	108 (5)	99 (15)	104 (10)
		1000	103 (13)	100 (2)	102 (9)	10	85 (5)	82 (7)	84 (6)	10	100 (4)	102 (10)	101 (6)
		2000	102 (10)	101 (2)	102 (7)	20	87 (10)	76 (5)	82 (10)	20	94 (7)	100 (10)	97 (8)
51	Phoxim	25	109 (14)	94 (4)	102 (13)	25	86 (10)	117 (2)	102 (17)	5	110 (13)	99 (3)	105 (12)
		50	100 (16)	96 (4)	98 (12)	50	82 (19)	79 (8)	81 (14)	10	94 (4)	102 (4)	98 (6)
		100	73 (14)	109 (3)	91 (20)	100	83 (3)	84 (3)	84 (3)	20	87 (10)	87 (20)	87 (13)
52	Fumagilin	5	113 (15)	102 (4)	108 (12)	5	99 (12)	119 (4)	109 (26)	5	94 (13)	86 (12)	90 (11)
		10	107 (12)	93 (8)	100 (12)	10	80 (6)	87 (6)	84 (10)	10	114 (12)	92 (11)	103 (13)
		20	106 (4)	99 (12)	103 (9)	20	78 (4)	75 (3)	77 (15)	20	97 (10)	98 (7)	98 (8)
53	Prednisolone	2	95 (7)	97 (10)	96 (8)	2	109 (5)	97 (13)	103 (11)	5	104 (19)	92 (12)	98 (15)
		4	105 (8)	85 (2)	95 (12)	4	78 (8)	93 (8)	86 (12)	10	111 (10)	98 (12)	105 (10)
		8	102 (8)	111 (4)	107 (7)	8	71 (2)	92 (4)	82 (14)	20	111 (6)	102 (3)	107 (5)
54	Florfenicol	100	-	-	-	150	114 (9)	115 (2)	115 (23)	50	92 (11)	99 (11)	96 (11)
		200	-	-	-	300	122 (3)	118 (1)	120 (5)	100	96 (5)	106 (6)	101 (7)
		400	-	-	-	600	111 (5)	95 (2)	103 (9)	200	107 (6)	104 (2)	106 (5)
54-1	Florfenicol amine	100	100 (4)	120 (2)	110 (10)	150	84 (3)	92 (1)	88 (27)	50	107 (13)	118 (1)	113 (19)
		200	107 (5)	108 (1)	108 (4)	300	79 (7)	114 (1)	97 (28)	100	102 (6)	92 (1)	97 (14)
		400	103 (5)	84 (0)	94 (11)	600	74 (4)	106 (1)	90 (24)	200	98 (2)	89 (1)	94 (14)
55	Fluralaner	5	107 (6)	91 (16)	99 (14)	5	106 (9)	105 (15)	106 (12)	30	110 (4)	99 (4)	105 (7)
		10	103 (6)	97 (17)	100 (10)	10	97 (4)	87 (13)	92 (11)	60	110 (4)	104 (6)	107 (5)
		20	100 (5)	102 (14)	101 (10)	20	106 (3)	72 (2)	89 (20)	120	101 (6)	97 (3)	99 (5)
56	Flumethasone	0.5	101 (17)	114 (7)	108 (14)	0.5	108 (14)	92 (5)	100 (14)	5	104 (15)	84 (8)	94 (16)
		1	91 (10)	83 (9)	87 (10)	1	85 (13)	71 (4)	78 (14)	10	108 (8)	94 (9)	101 (10)
		2	98 (10)	95 (4)	97 (8)	2	72 (4)	65 (4)	69 (7)	20	107 (11)	98 (6)	103 (9)
57	tau-fluvalinate	5	116 (9)	89 (16)	103 (18)	5	91 (6)	117 (4)	104 (15)	5	95 (17)	95 (12)	95 (14)
		10	98 (4)	110 (15)	104 (13)	10	82 (11)	86 (6)	84 (15)	10	83 (17)	106 (7)	95 (14)
		20	100 (6)	94 (19)	97 (13)	20	80 (7)	80 (4)	80 (16)	20	76 (8)	96 (7)	86 (13)
58	Piperazine	150	112 (11)	96 (3)	104 (13)	150	112 (3)	-	-	50	105 (4)	-	-
		300	111 (11)	108 (1)	110 (10)	300	98 (7)	-	-	100	95 (15)	-	-
		600	116 (9)	101 (1)	109 (11)	600	80 (3)	-	-	200	92 (10)	-	-
59	2-Hydroxy-4,6,dimethyl-pyrimidine	5	84 (2)	-	-	5	114 (3)	-	-	5	-	-	-
		10	88 (7)	-	-	10	101 (13)	-	-	10	-	-	-
		20	99 (15)	-	-	20	86 (8)	-	-	20	-	-	-

Table 3. Inter-laboratory validation results of analytical method for egg and milk.

No.	Compounds	Egg				Milk			
		Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5		
			Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.
1	Gamithromycin	5	101 (12)	96 (2)	99 (13)	5	85 (13)	90 (20)	88 (20)
		10	96 (7)	99 (2)	98 (16)	10	89 (7)	105 (16)	97 (17)
		20	80 (13)	103 (3)	92 (13)	20	103 (4)	104 (6)	104 (9)
2	Guaifenesin	5	103 (7)	90 (8)	97 (10)	5	112 (25)	77 (8)	95 (28)
		10	96 (6)	98 (8)	97 (7)	10	84 (25)	105 (4)	95 (19)
		20	101 (4)	100 (5)	101 (6)	20	93 (10)	118 (1)	106 (14)
3	Narasin	3	92 (9)	-	-	5	86 (21)	94 (7)	90 (15)
		6	110 (2)	-	-	10	102 (8)	95 (10)	99 (9)
		30	111 (6)	-	-	20	102 (6)	100 (10)	101 (8)
4	Nitroxoline	5	84 (16)	116 (4)	100 (19)	5	110 (7)	104 (4)	107 (6)
		10	102 (10)	95 (2)	99 (8)	10	88 (13)	77 (6)	83 (15)
		20	102 (10)	95 (3)	99 (8)	20	72 (12)	88 (16)	80 (16)
5	Naftazone	5	110 (8)	101 (4)	106 (12)	5	79 (11)	86 (17)	83 (14)
		10	101 (12)	103 (3)	102 (8)	10	93 (7)	85 (12)	89 (13)
		20	91 (10)	100 (4)	96 (10)	20	97 (5)	91 (4)	94 (13)
6	Nitroxynil	5	98 (7)	104 (10)	101 (8)	5	105 (9)	91 (16)	98 (17)
		10	98 (6)	100 (4)	99 (8)	10	100 (8)	101 (8)	101 (8)
		20	83 (10)	106 (4)	95 (12)	20	100 (8)	86 (7)	93 (14)
7	Decoquinate	5	99 (14)	90 (4)	95 (10)	5	93 (15)	93 (15)	93 (16)
		10	96 (8)	89 (3)	93 (11)	10	94 (17)	95 (7)	95 (11)
		20	85 (6)	98 (3)	92 (9)	20	107 (5)	83 (9)	95 (14)
8	Dehydrocholic acid	5	98 (5)	101 (5)	100 (5)	5	138 (8)	84 (8)	111 (78)
		10	100 (7)	99 (6)	100 (11)	10	92 (14)	97 (15)	95 (73)
		20	99 (8)	106 (2)	103 (9)	20	91 (9)	101 (11)	96 (73)
9	Dexamethasone	0.05	95 (23)	101 (9)	98 (16)	0.15	86 (20)	104 (12)	95 (18)
		0.1	87 (22)	97 (4)	92 (15)	0.3	89 (16)	102 (32)	96 (26)
		0.2	82 (18)	102 (6)	92 (16)	0.6	86 (8)	114 (18)	100 (20)
10	Doramectin	5	103 (15)	-	-	8	103 (24)	87 (19)	95 (19)
		10	74 (4)	-	-	15	91 (15)	109 (8)	100 (19)
		20	78 (8)	-	-	30	100 (9)	93 (13)	97 (27)
11	Dichlorvos	5	93 (7)	115 (3)	104 (12)	10	89 (13)	109 (3)	99 (13)
		10	104 (13)	75 (3)	90 (20)	20	91 (6)	118 (1)	105 (14)
		20	98 (10)	92 (4)	95 (8)	40	104 (5)	84 (1)	94 (12)
12	Lubabegron	5	101 (8)	97 (4)	99 (6)	5	95 (4)	97 (5)	96 (5)
		10	99 (10)	75 (3)	87 (19)	10	95 (5)	96 (2)	96 (5)
		20	102 (6)	77 (4)	90 (17)	20	98 (4)	96 (4)	97 (4)
13	Maduramycin	2	94 (4)	92 (8)	93 (16)	5	93 (7)	97 (4)	95 (20)
		4	73 (2)	89 (7)	81 (12)	10	107 (6)	93 (8)	100 (8)
		20	75 (3)	100 (11)	88 (20)	20	102 (7)	81 (9)	92 (12)
14	Methomidate	5	97 (17)	98 (4)	98 (13)	5	99 (7)	83 (14)	91 (16)
		10	107 (19)	101 (4)	104 (11)	10	95 (13)	92 (17)	94 (11)
		20	118 (17)	102 (4)	110 (12)	20	101 (8)	98 (10)	100 (7)

No.	Compounds	Egg				Milk			
		Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5		
			Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.
15	Methyl benzoquate	5	104 (8)	98 (1)	101 (8)	5	98 (5)	88 (17)	93 (13)
		10	98 (8)	95 (2)	97 (10)	10	92 (7)	103 (4)	98 (8)
		20	91 (5)	95 (2)	93 (11)	20	93 (3)	90 (11)	92 (8)
16	Monensin	5	94 (23)	101 (10)	98 (16)	5	81 (16)	97 (13)	89 (18)
		10	79 (17)	98 (3)	89 (18)	10	97 (15)	92 (13)	95 (16)
		20	82 (11)	101 (4)	92 (12)	20	102 (4)	97 (7)	100 (14)
17	Buparvaquone	5	101 (12)	105 (7)	103 (9)	5	93 (24)	89 (8)	91 (15)
		10	93 (4)	104 (12)	99 (10)	10	107 (13)	109 (6)	108 (13)
		20	82 (5)	109 (9)	96 (14)	20	109 (9)	101 (13)	105 (21)
18	Cyromazine	100	93 (6)	90 (1)	92 (13)	5	108 (14)	107 (4)	108 (10)
		200	104 (3)	108 (1)	106 (15)	10	87 (25)	96 (3)	92 (17)
		400	115 (2)	112 (1)	114 (12)	20	90 (9)	86 (1)	88 (7)
19	Salinomycin	10	92 (16)	100 (2)	96 (11)	5	101 (12)	86 (15)	94 (17)
		20	96 (7)	98 (2)	97 (10)	10	104 (6)	91 (15)	98 (11)
		40	99 (8)	94 (1)	97 (11)	20	104 (6)	91 (11)	98 (9)
20	Cefacetrile	5	-	97 (30)	-	25	97 (18)	114 (6)	106 (14)
		10	-	75 (25)	-	50	101 (8)	92 (3)	97 (7)
		20	-	73 (27)	-	100	98 (5)	76 (4)	87 (14)
21	Cephapirin	5	105 (3)	100 (8)	103 (6)	15	97 (10)	95 (4)	96 (7)
		10	98 (3)	99 (6)	99 (5)	30	102 (5)	100 (2)	101 (4)
		20	96 (6)	98 (3)	97 (4)	60	101 (5)	101 (1)	101 (3)
21-1	Desacetyl cephapirin	50	85 (19)	120 (2)	103 (20)	15	83 (10)	88 (9)	86 (10)
		10	79 (7)	80 (6)	80 (6)	30	100 (21)	100 (4)	100 (15)
		20	88 (6)	97 (2)	93 (7)	60	92 (12)	101 (5)	97 (10)
22	Cefalonium	5	99 (1)	100 (10)	100 (12)	5	102 (10)	124 (2)	113 (23)
		10	104 (2)	89 (8)	97 (10)	10	97 (21)	95 (3)	96 (28)
		20	106 (4)	89 (8)	98 (9)	20	103 (3)	76 (2)	90 (22)
23	Ceftiofur	5	108 (17)	102 (5)	105 (12)	50	79 (9)	111 (1)	95 (18)
		10	98 (20)	79 (9)	89 (18)	100	95 (5)	90 (2)	93 (10)
		20	104 (13)	93 (5)	99 (11)	200	99 (6)	104 (2)	102 (9)
23-1	Desfuroyl ceftiofur	5	-	-	-	50	-	94 (7)	-
		10	-	-	-	100	-	99 (7)	-
		20	-	-	-	200	-	62 (4)	-
24	Cymiazole	5	79 (23)	89 (3)	84 (13)	5	98 (15)	76 (2)	87 (19)
		10	107 (12)	100 (3)	104 (8)	10	98 (16)	107 (2)	103 (19)
		20	95 (4)	105 (5)	100 (9)	20	89 (14)	120 (1)	105 (14)
25	Aminopyrine	5	112 (10)	109 (6)	111 (13)	5	114 (11)	-	-
		10	97 (27)	94 (19)	96 (18)	10	109 (21)	-	-
		20	87 (10)	90 (10)	89 (12)	20	119 (2)	-	-
26	Amitraz	5	74 (20)	103 (2)	89 (20)	5	81 (29)	84 (20)	83 (25)
		10	83 (27)	84 (6)	84 (18)	10	100 (20)	94 (9)	97 (17)
		20	111 (18)	96 (6)	104 (11)	20	111 (20)	102 (18)	107 (16)

No.	Compounds	Egg				Milk			
		Fortification (ng g⁻¹)	Recovery (CV), n=5			Fortification (ng g⁻¹)	Recovery (CV), n=5		
			Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.
26-1	2,4-dimethylaniline	5	93 (18)	111 (10)	102 (16)	5	-	116 (3)	-
		10	100 (11)	106 (9)	103 (10)	10	-	115 (8)	-
		20	93 (13)	104 (3)	99 (11)	20	-	87 (9)	-
27	Abamectin	5	109 (23)	96 (15)	103 (17)	5	101 (18)	97 (19)	99 (15)
		10	109 (17)	76 (8)	93 (22)	10	94 (8)	101 (9)	98 (12)
		20	119 (17)	77 (3)	98 (23)	20	100 (7)	84 (16)	92 (17)
28	Acrinol	5	103 (6)	121 (1)	112 (25)	5	99 (16)	98 (13)	99 (11)
		10	90 (8)	121 (3)	106 (42)	10	82 (25)	93 (16)	88 (19)
		20	82 (11)	117 (2)	100 (35)	20	100 (4)	95 (17)	98 (12)
29	Anthralic acid	5	103 (6)	103 (1)	103 (4)	5	118 (14)	99 (14)	109 (16)
		10	107 (6)	81 (1)	94 (16)	10	86 (23)	94 (16)	90 (19)
		20	104 (4)	97 (2)	101 (5)	20	94 (13)	79 (12)	87 (15)
30	Ampurolium	5	99 (12)	90 (11)	95 (11)	5	109 (13)	116 (2)	113 (9)
		10	98 (29)	94 (8)	96 (17)	10	91 (14)	106 (4)	99 (12)
		20	98 (16)	99 (6)	99 (9)	20	94 (7)	98 (14)	96 (11)
31	Ethoxyquin	5	108 (20)	98 (13)	103 (17)	5	92 (26)	75 (4)	84 (22)
		10	75 (9)	94 (7)	85 (14)	10	95 (14)	90 (2)	93 (10)
		20	89 (17)	100 (3)	95 (13)	20	93 (17)	107 (6)	100 (13)
31-1	Ethoxyquin dimer	5	102 (16)	86 (7)	94 (16)	5	96 (13)	104 (16)	100 (12)
		10	86 (19)	72 (3)	79 (22)	10	102 (12)	89 (5)	96 (10)
		20	102 (9)	80 (6)	91 (12)	20	112 (6)	102 (7)	107 (12)
32	Eprinomectin	5	103 (19)	98 (1)	101 (20)	10	120 (8)	98 (15)	109 (25)
		10	114 (18)	98 (5)	106 (18)	20	115 (15)	106 (12)	111 (15)
		20	107 (12)	99 (2)	103 (13)	40	108 (5)	98 (3)	103 (7)
33	Iodo hydroxy quinoline sulfonic acid	5	87 (8)	101 (18)	94 (16)	5	106 (13)	112 (7)	109 (17)
		10	95 (7)	104 (5)	100 (17)	10	98 (17)	109 (19)	104 (18)
		20	83 (4)	99 (9)	91 (20)	20	101 (8)	77 (16)	89 (15)
34	Ivermectin	5	109 (27)	99 (14)	104 (26)	5	115 (20)	90 (11)	103 (21)
		10	90 (29)	74 (6)	82 (22)	10	94 (14)	100 (8)	97 (11)
		20	117 (17)	81 (3)	99 (20)	20	98 (8)	97 (15)	98 (11)
35	β-Zeranol	5	77 (15)	101 (2)	89 (16)	5	102 (3)	105 (10)	104 (9)
		10	86 (22)	97 (6)	92 (18)	10	90 (14)	89 (12)	90 (12)
		20	89 (16)	98 (3)	94 (14)	20	93 (8)	93 (6)	93 (10)
36	α-Zeranol	5	110 (9)	99 (6)	105 (10)	5	96 (14)	103 (7)	100 (11)
		10	97 (16)	93 (9)	95 (13)	10	88 (10)	103 (5)	96 (10)
		20	94 (9)	89 (5)	92 (15)	20	88 (10)	94 (5)	91 (13)
37	Zoalene	5	93 (14)	104 (12)	99 (14)	5	114 (17)	83 (4)	99 (21)
		10	102 (8)	113 (12)	108 (11)	10	95 (25)	93 (15)	94 (19)
		20	99 (2)	103 (7)	101 (5)	20	80 (13)	80 (6)	80 (11)
37-1	3-ANOT	5	103 (17)	105 (7)	104 (10)	5	118 (12)	81 (4)	100 (19)
		10	98 (14)	100 (9)	99 (12)	10	102 (20)	96 (7)	99 (12)
		20	93 (15)	101 (2)	97 (12)	20	92 (10)	98 (9)	95 (13)

No.	Compounds	Egg				Milk			
		Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5		
			Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.
38	Medroxy progesterone acetate	1	114 (21)	96 (13)	105 (20)	3	78 (12)	92 (18)	85 (17)
		2	108 (15)	100 (2)	104 (11)	6	85 (15)	96 (16)	91 (16)
		8	118 (15)	100 (5)	109 (14)	30	94 (8)	93 (14)	94 (11)
39	Melengestrol acetate	5	115 (15)	98 (3)	107 (10)	5	107 (14)	105 (16)	106 (12)
		10	98 (14)	95 (3)	97 (10)	10	91 (19)	84 (21)	88 (17)
		20	96 (9)	100 (1)	98 (7)	20	89 (7)	86 (10)	88 (8)
40	Trenbolone acetate	5	101 (8)	100 (6)	101 (8)	5	94 (7)	79 (6)	87 (11)
		10	105 (6)	81 (4)	93 (15)	10	92 (5)	91 (13)	92 (8)
		20	101 (12)	81 (7)	91 (13)	20	95 (9)	105 (10)	100 (9)
41	Clanobutin	5	111 (4)	100 (2)	106 (6)	5	84 (11)	83 (14)	84 (13)
		10	102 (9)	101 (1)	102 (6)	10	101 (4)	90 (9)	96 (8)
		20	92 (6)	100 (2)	96 (5)	20	108 (2)	75 (7)	92 (16)
42	Chlorpyrifos	5	114 (26)	96 (12)	105 (27)	10	118 (8)	103 (6)	111 (10)
		10	119 (27)	108 (4)	114 (20)	20	115 (13)	102 (14)	109 (12)
		20	117 (9)	105 (6)	111 (10)	40	118 (7)	86 (13)	102 (16)
43	Tolfenamic acid	5	101 (5)	96 (1)	99 (4)	25	82 (8)	78 (12)	80 (10)
		10	104 (6)	107 (8)	106 (6)	50	96 (7)	97 (10)	97 (9)
		20	104 (4)	118 (2)	111 (6)	100	105 (6)	93 (11)	99 (11)
44	Triamcinolone	5	105 (9)	96 (3)	101 (7)	5	76 (5)	114 (10)	95 (22)
		10	106 (11)	105 (4)	106 (6)	10	78 (6)	90 (6)	84 (9)
		20	105 (6)	107 (4)	106 (5)	20	79 (4)	98 (4)	89 (12)
45	Thiophanate	5	112 (21)	95 (3)	104 (18)	5	91 (17)	110 (7)	101 (17)
		10	102 (15)	75 (14)	89 (21)	10	99 (16)	96 (12)	98 (11)
		20	76 (41)	74 (6)	75 (17)	20	100 (11)	111 (3)	106 (7)
46	Tylvalosin	5	99 (4)	100 (2)	100 (4)	5	92 (13)	86 (5)	89 (10)
		10	104 (9)	89 (2)	97 (13)	10	92 (12)	114 (2)	103 (13)
		20	93 (8)	87 (2)	90 (8)	20	95 (11)	112 (5)	104 (12)
46-1	3-AT	5	93 (7)	98 (2)	96 (6)	5	91 (6)	98 (11)	95 (12)
		10	109 (11)	86 (1)	98 (15)	10	94 (17)	93 (16)	94 (14)
		20	114 (9)	81 (5)	98 (19)	20	113 (9)	95 (6)	104 (12)
47	Phenothiazine	5	99 (22)	83 (6)	91 (19)	5	83 (18)	102 (16)	93 (19)
		10	75 (10)	81 (9)	78 (10)	10	89 (17)	87 (17)	88 (16)
		20	97 (17)	89 (11)	93 (15)	20	83 (10)	84 (18)	84 (14)
48	Phenylbutazone	5	102 (11)	101 (7)	102 (8)	5	106 (12)	85 (9)	96 (16)
		10	94 (5)	77 (6)	86 (15)	10	92 (14)	115 (4)	104 (15)
		20	91 (7)	94 (5)	93 (8)	20	96 (17)	103 (5)	100 (12)
49	Pentamethylene tetrazol	5	95 (2)	116 (3)	106 (11)	5	76 (14)	96 (6)	86 (16)
		10	102 (3)	120 (2)	111 (9)	10	101 (15)	96 (15)	99 (14)
		20	98 (5)	118 (1)	108 (10)	20	109 (7)	88 (5)	99 (13)
50	Phosmet	5	82 (7)	-	-	5	92 (10)	81 (8)	87 (9)
		10	81 (9)	-	-	10	90 (16)	82 (7)	86 (13)
		20	97 (14)	-	-	20	99 (5)	91 (3)	95 (12)

No.	Compounds	Egg				Milk			
		Fortification (ng g^{-1})	Recovery (CV), n=5			Fortification (ng g^{-1})	Recovery (CV), n=5		
			Lab. A	Lab. B	Inter-Lab.		Lab. A	Lab. B	Inter-Lab.
51	Phoxim	5	96 (9)	104 (4)	100 (8)	5	119 (10)	94 (6)	107 (13)
		10	96 (8)	105 (3)	101 (7)	10	98 (13)	89 (5)	94 (10)
		20	99 (5)	90 (2)	95 (6)	20	116 (9)	79 (7)	98 (22)
52	Fumagilin	5	95 (14)	82 (18)	89 (19)	5	110 (21)	96 (15)	103 (17)
		10	81 (10)	81 (25)	81 (25)	10	97 (8)	95 (7)	96 (10)
		20	86 (4)	94 (32)	90 (20)	20	103 (3)	75 (9)	89 (17)
53	Prednisolone	5	83 (18)	99 (7)	91 (14)	3	103 (16)	107 (15)	105 (14)
		10	101 (11)	98 (3)	100 (8)	6	103 (9)	100 (8)	102 (8)
		20	94 (19)	96 (3)	95 (11)	12	91(3)	103 (5)	97 (7)
54	Florfenicol	5	109 (26)	103 (10)	106 (8)	5	93 (22)	86 (14)	90 (18)
		10	93 (11)	103 (4)	98 (5)	10	79 (18)	94 (12)	87 (17)
		20	70 (26)	103 (2)	87 (3)	20	81 (11)	93 (10)	87 (12)
54-1	Florfenicol amine	5	-	112 (8)	-	5	101 (13)	102 (3)	102 (8)
		10	-	119 (2)	-	10	85 (23)	100 (3)	93 (16)
		20	-	105 (2)	-	20	75 (5)	97 (1)	86 (13)
55	Fluralaner	650	101 (9)	100 (1)	101 (6)	5	119 (14)	96 (9)	108 (17)
		1300	94 (8)	105 (4)	100 (8)	10	97 (13)	92 (11)	95 (13)
		2600	70 (4)	102 (5)	86 (20)	20	97 (8)	95 (5)	96 (14)
56	Flumethasone	5	88 (22)	108 (11)	98 (15)	0.5	86 (18)	89 (13)	88 (15)
		10	94 (24)	80 (8)	87 (19)	1	89 (8)	117 (18)	103 (20)
		20	100 (10)	79 (8)	90 (15)	2	93 (13)	115 (8)	104 (15)
57	tau-fluvalinate	5	93 (5)	-	-	5	100 (6)	90 (18)	95 (13)
		10	96 (3)	-	-	10	98 (12)	97 (10)	98 (10)
		20	95 (3)	-	-	20	102 (7)	104 (11)	103 (8)
58	Piperazine	1000	110 (3)	110 (1)	110 (2)	25	86 (8)	100 (2)	93 (10)
		2000	102 (3)	81 (1)	92 (13)	50	93 (8)	95 (1)	94 (5)
		4000	99 (6)	110 (1)	105 (7)	100	83 (9)	94 (1)	89 (8)
59	2-Hydroxy-4,6,dimethyl-pyrimidine	5	119 (16)	92 (12)	106 (17)	5	95 (13)	91 (24)	93 (16)
		10	99 (21)	103 (6)	101 (12)	10	79 (24)	89 (11)	84 (16)
		20	118 (12)	104 (2)	111 (10)	20	82 (9)	87 (14)	85 (20)

the recoveries and CV at the MRL and LOQ were compared by filtration type. As shown in Fig. 3, the lowest numbers of analytes were observed in PTFE filtered beef and chicken samples, and PVDF filtered egg and milk samples. In particular, without filtration, the final egg extracts could not be analyzed because of the concerns about contamination of the analysis device, and also it could not be filtered with a PVDF filter. On the other hand, nylon retained the largest number of analytes during filtration.

Method validation

Table 2 and Table 3 summarizes the recovery and CV for each veterinary drug in the five matrices. A calibration curve was generated for all reference standards using matrix-matched calibrations at 6 target concentrations (blank, 0.25, 0.5, 1, 2, and 4× MRL; 2.5, 5, 10, 20, and 40 μg kg^{-1}; and blank, 1, 2, 5, 10, and 20× LOQ). Matrix effects are inevitable in LC-MS/MS analysis. Matrix-matched calibration curves were generated to offset this effect. The quantification of analytes in the samples was performed by spiking on blank samples before extraction with the target compounds at different concentrations. The calibration curves showed good linearity with determination coefficients (r^2) above 0.98 in all cases. Accuracy and precision

Table 4. The LOD (ng g^{-1}) and LOQ (ng g^{-1}) in livestock products

Compound	Beef		Pork		Chicken		Egg		Milk	
	LOD	LOQ	LOD	LOQ	LOD	LOQ	LOD	LOQ	LOD	LOQ
Gamithromycin	3.4	8.3	2.3	4.8	0.3	1.3	1.9	6.2	1.5	3.2
Guaifenesin	24.1	79.4	5.6	18.6	0.6	2.1	1.3	4.3	2	6.8
Narasin	2.6	8.6	3.1	10.2	3.4	11.1	3.7	12.1	1.4	4.5
Nitroxoline	10	30.3	4.4	14.6	7	23.1	73.9	243.9	4.1	13.6
Naftazone	0.8	2.7	0.4	1.2	0.3	1.1	0.3	1.1	0.6	2.1
Nitroxynil	16.7	55.1	3.6	11.8	0.6	2	1.2	3.9	0.3	0.9
Decoquinate	0.3	0.9	0.2	0.7	0.7	1.7	0.2	0.8	0.2	0.7
Dehydrocholic acid	11	36.3	9.1	30.2	8.1	26.7	3.8	12.5	8.7	28.7
Dexamethasone	1	3.2	2.4	8	2.2	7.3	2.7	9.1	0.6	2
Doramectin	3.4	11.1	1.9	6.4	0.3	0.8	2.2	7.1	0.3	0.6
Dichlorvos	7.2	23.9	-	-	12.5	3.8	2.5	4.8	1.5	5
Lubabegron	0.2	0.5	1.2	4	0.1	0.2	0.2	0.6	0.1	0.4
Maduramycin	0.8	2.6	0.3	1.1	0.8	1.9	0.5	1.6	2.5	1
Methomidate	0.2	0.8	0.4	1.2	0.6	1.8	0.5	1.6	0.5	1.6
Methylbenzuquate	0.1	0.4	0.1	0.3	0.1	0.4	0.2	0.7	0.1	0.4
Monensin	0.2	0.8	1.5	4.9	0.6	1.8	0.8	2.7	1.4	4.6
Buparvaquone	1.5	5	3.2	10.6	1.4	4.6	2.4	7.9	0.8	2.6
Cyromazine	14.6	48.3	8.3	27.5	13.8	45.5	17.6	57.9	0.9	0.8
Salinomycin	1.7	5.5	0.9	3	0.3	1.1	2.6	8.4	1.5	4.9
Cefacetrile	59.8	197.4	10.5	34.7	15.5	51.2	0.5	0.8	11.1	19.9
Cephapirin	5.2	17.1	0.4	1.4	1.1	3.7	0.3	0.8	4.1	13.6
Desacetyl cephapirin	5.5	18	3.9	12.9	2.1	6.9	1.3	4.3	1.3	4.4
Cefalonium	1.6	5.4	3.2	10.6	0.9	3.1	0.5	1.8	2	6.5
Ceftiofur	2.7	8.8	2.6	8.5	1	3.3	1.5	5	2.7	8.7
Desfuroyl ceftiofur	149.1	492.2	308.9	1019.4	231	762.3	339.3	1119.6	1.3	4
Cymiazole	0.5	1.6	1.2	1.7	0.2	0.8	0.7	2.3	0.1	0.5
Aminopyrine	6.7	22	3.9	12.8	1.1	3.8	0.7	2.2	1	3.2
Amitraz	23.9	78.8	-	-	20.6	67.9	1.8	5.8	2.5	0.8
2,4-dimethylaniline	5.7	10.7	14.5	47.9	3.4	11.1	3.2	10.7	1.9	0.6
Abamectin	3.1	10.3	1.2	2.7	1.7	5.5	1.9	6.4	0.4	1.3
Acrinol	0.4	1.4	0.2	0.6	0.3	1.4	2.5	5.8	0.4	1.2
Anthralic acid	0.8	2.7	0.6	2.1	1.2	2.1	3.7	12.1	1.1	3.5
Ampurolium	163.7	540.2	2.5	8.4	1.4	2.8	0.7	2.1	1.3	4.4
Ethoxyquin	2.5	5.3	5.1	17	1.2	3.9	2.5	4.3	2.5	4.1
Ethoxyquin dimer	1.5	5	0.5	1.5	0.1	0.4	0.3	1.1	0.4	1.2
Eprinomectin	0.7	2.4	3.7	12.3	0.9	2.8	2.1	7	2.8	9.4
Iodo hydroxy quinoline sulfonic acid	0.8	2.5	1.2	2.5	1.1	3.7	1.2	4	1.5	4.8
Ivermectin	7.8	25.7	4.7	15.6	2.6	8.7	1.5	4.9	1	3.4
α-Zeranol	1.9	6.3	1.4	4.8	1.4	4.5	0.8	2.5	3.6	11.7
β-Zeranol	2.8	9.1	2.5	8.3	0.8	2.6	0.9	2.9	3.1	10.3
Zoalene	0.6	1.9	6	19.7	140.8	464.7	0.1	0.3	7.1	23.5
3-ANOT	3.2	10.6	4.2	14	3.9	12.9	2	6.5	1.4	4.7
Medroxyprogesterone acetate	0.4	1.2	0.7	2.2	0.4	0.9	0.4	1.4	0.6	2
Melengestrol acetate	1	3.2	5.9	19.3	1.6	5.3	0.6	2	0.5	1.6
Trenbolone acetate	0.6	2.1	1.7	1.7	0.9	3.1	1.3	4.2	1.2	4.1

Compound	Beef		Pork		Chicken		Egg		Milk	
	LOD	LOQ	LOD	LOQ	LOD	LOQ	LOD	LOQ	LOD	LOQ
Clanobutin	0.2	0.6	0.4	1.4	0.2	0.7	0.3	1.1	0.5	1.5
Chlorpyrifos	3.2	2.9	2.3	7.2	1.3	2.3	1.5	4.8	2.8	7.5
Tolfenamic acid	0.8	1.8	2.2	5	0.4	1.4	1.4	4.8	1.4	4.7
Triamcinolone	1.4	4.3	0.5	2	0.8	2.7	2	6.6	3.2	10.7
Thiophanate	0.3	1.1	0.3	1.1	0.2	0.8	2	6.6	0.7	2.5
Tylvalosin	1.4	4.8	2.7	8.9	0.7	2.4	1.6	5.4	0.6	1.8
Tylosin-3-acetate	0.9	3.1	1.4	4.5	0.5	1	0.7	1.5	1	0.9
Phenothiazine	8.8	29	7.2	23.8	0.2	0.8	2	6.6	1.4	4.8
Phenylbutazone	1.2	4.1	0.7	2.4	1.8	6	0.7	2.3	1.4	4.6
Pentamethylene tetrazol	2.3	7.7	5.7	18.9	2.6	8.7	2	6.5	4.7	15.6
Phosmet	1.7	5.6	0.1	0.4	0.1	0.4	0.3	0.9	0.2	0.7
Phoxim	0.4	1.4	1.7	4.5	1.2	4	2.2	7.2	1	3.3
Fumagilin	2.9	9.6	3.2	10.4	4	13.1	3.9	12.9	1.8	6
Prednisolone	9.8	32.4	2.9	9.4	1.3	4.1	1.4	4.6	0.9	2.9
Florfenicol	2	6.4	2.9	9.7	0.7	2.5	21.1	69.5	3.3	10.9
Florfenicol amine	2.6	8.7	336	1108.8	14.2	46.9	1.8	0.5	5.4	17.9
Fluralaner	1	3.3	1.8	5.8	0.5	1.7	32.5	98.5	0.3	0.9
Flumethasone	5.9	19.6	3.2	1.4	2	6.5	2.6	8.6	1.5	4.8
tau-Fluvalinate	1.6	5.3	0.9	3.1	0.4	1.4	1.8	5.9	0.4	1.3
Piperazine	25.5	84.1	6.3	20.7	10.5	34.7	5.6	18.3	3.6	12
2-Hydroxy-4,6,-dimethylpyrimidine	0.5	0.8	1.5	3.1	0.3	0.4	1.5	1.4	0.8	2.8

were examined at three different concentrations (0.5, 1, and 2× MRL, or 5, 10, and 20 μg kg^{-1} and 1, 2, and 10× LOQ) for all matrices. The intra- and inter-laboratory validation results were in compliance with Codex guidelines (CAC/GL 71-2009). Recoveries of >88.1% in beef and milk and >83.6% in pork and eggs were achieved for the tested veterinary drugs with satisfactory CV. A total of 52 out of 67 compounds (77.6%) in chicken showed the proper method validation results. Table 4 shows the LOD and LOQ results for livestock products. The LOD and LOQ were determined based on analyte sensitivity (S/N ratio ≥3 or ≥10, respectively) in livestock products. The LODs were between 0.1 and 339.3 ng g^{-1} for different compounds, while the LOQs ranged from 0.2 to 1119.6 ng g^{-1}.

Application to real samples

To evaluate the applicability of the proposed method for routine analysis, five different types of highly consumed livestock products were obtained from local supermarkets. Livestock product samples (65 beef, 112 pork, 56 chicken, 61 egg, and 73 milk) were transferred to our laboratory and analyzed according to the optimized procedure. Table 5 summarizes the quantified results of the sample. Three compounds (maduramycin, anthranilic acid, and fluralaner) were detected in livestock product samples. In our 367 samples, three samples (0.8%) were detected. The detected concentrations ranged from 10 to 560 ng g^{-1}. Maduramycin, anthranilic acid, and fluralaner have been approved for use in Korea. No compound was detected or quantitated, which would exceed the MRL established in Korea. Therefore, further investigation of the incurred samples is required to assess the extraction efficiency of the current analytical method.

Conclusions

A comprehensive and efficient multi-residue analytical method for the simultaneous determination of 66 compounds (59 veterinary drugs and 7 metabolites) in livestock products using LC-MS/MS was developed. The developed sample extraction method from different livestock matrices and clean-up steps were easy, rapid, and effective, and also minimized analyte loss during sample preparation. Furthermore, the use of UHPLC technology shortened the analysis times for all analytes. LC-MS/MS offers the best performance for

Table 5. The concentration (ng g^{-1}) of compounds in real sample analysis

Species	Sample number	Detected number	Compounds	Concentrations (ng g^{-1})
Beef	65	-	n.d	-
Pork	112	1	Anthranilic acid	10
Chicken	56	1	Maduramycin	94
Egg	61	1	Fluralaner	560
Milk	73	-	n.d	-

screening purposes and can effectively provide concentration values. It is sufficiently accurate to differentiate between detection sample and blank samples or drug concentrations below or above the MRL.

Note

The authors declare no conflict of interest.

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