TECHNICAL OPERATING PROCEDURE

PROCEDURE TITLE: Determination of Oxytetracycline (OTC) in the Edible Tissue of Fish Fillets

AREA OF APPLICABILITY:

A. This procedure is applicable to all areas of the Chemistry and Physiology Branch at the Upper Midwest Environmental Sciences Center (UMESC).

B. The FDA reviewed this HPLC method and concluded that it can be used in place of the microbiological assay provided that the performing lab can meet the performance criteria established in the bridging study conducted by Stehly and Gingerich [1,2].

C. Method validation parameters

1. Accuracy, precision, and sensitivity of the analytical method (OTC free base) for 8 species of fish[3]

Type of Edible Fillet	Level (ng/g)	Accuracy (% Recovery)	Precision (%RSD)	MDL (ng/g)	LOQ (ng/g)
Atlantic Salmon[4,5]	1000	85.0	1.8	4	13
Atlantic Salmon[4,5]	5000	84.6	1.5	4	13
Striped Bass[4,5]	1000	86.8	1.6	6	22
Striped Bass[4,5]	5000	85.5	0.9	6	22
White Sturgeon[4,5]	1000	89.9	1.9	3	10
White Sturgeon[4,5]	5000	87.5	1.2	3	10
Rainbow Trout[4,5]	1000	83.2	2.1	4	12
Rainbow Trout[4,5]	5000	84.9	2.7	4	12
Channel Catfish[4,5]	1000	86.0	5.8	3	9
Channel Catfish[4,5]	5000	89.8	1.9	3	9
Walleye[4,5]	1000	86.8	5.0	2	6
Walleye[4,5]	5000	86.4	2.5	2	6
Northern Pike[6]	1002	90	2.3	2.8	9.5
Northern Pike[6]	2004	91	2.8	2.8	9.5

Northern Pike[6]	**4008**	**89**	**7.3**	**2.8**	**9.5**
Coho Salmon[6]	**1024**	**94**	**3.4**	**3.8**	**13**
Coho Salmon[6]	**2048**	**92**	**2.8**	**3.8**	**13**
Coho Salmon[6]	**4008**	**90.8**	**1.1**	**3.8**	**13**

2. HPLC detector response linearity[5,6]: 3.16 - 50,000 ng/mL OTC free base

3. The instruments used to conduct validation tests are listed in UMESC studies CAP-95-00084-01[6] and CAP-98-00084-04[6].

4. The method may be used to analyze samples outside of the validated parameters, however, the analyst should evaluate the new conditions and validate the method for critical conditions outside of the stated parameters.

PRINCIPLE: This method works by cleaning sample using reverse phase SPE and isolating OTC using reverse phase HPLC. OTC is quantified by measuring the amount of light absorbed at 355 nm wavelength and comparing the results to a set of standards. This method is performance based. It is not permitted to modify or omit any critical point(s) or quality control step(s). It is permitted to modify or omit any non-critical point(s) if it can be demonstrated that the modified method produces results equivalent or superior to results produced by this method.

PRECAUTIONS:

A. Potential Interferences

1. Necessary precautions must be taken to minimize the possibility of contamination.

2. When present, sulfadimethoxine sodium salt (a component of Romet 30™) may interfere with OTC analysis since it chromatographs to within 0.5 minutes of OTC.

3. Whenever possible, direct OTC contact with metallic materials should be avoided because OTC is capable of complexing with metal ions.

4. Analysts must refer to the SOP for each item or procedure used for additional potential interferences.

B. Safety

1. Standard laboratory safety devices (lab coat, gloves and safety glasses) should always be worn when carrying out the described procedures.

2. Material Safety Data Sheets (MSDS) must be followed for solvents and chemicals used in this procedure.

3. Analysts must refer to the SOP for each item or procedure used for additional safety precautions.

PROCEDURE:

A. Apparatus (Equivalent apparatus may be used where appropriate)

1. *HPLC system* - System with UV detector response linear over range of 3.16-50000 ng/mL OTC (HP 1090 Liquid Chromatograph, Series II, Agilent Technologies Inc., Palo Alto, CA)

2. *HPLC column* - Analytical column, C_{18}, 250 x 4.6 mm, 5 µm with matching guard column (ODS-A and ODS-AQ, YMC, Inc., Wilmington, NC). Two lots of ODS-A and two lots of ODS-AQ columns have been tested. Other brands of columns have not been tested and may have different separation characteristics.

3. *Mechanical homogenizer* - Capable of homogenizing frozen, ground fish fillet (VirTishear Tempest I.Q. with macro open blade shaft assembly and macro blades, Virtis, Gardiner, NY)

4. *Microliter syringe* - Hamilton 800 series (Hamilton, Reno, NV)

5. *Analytical Balance for standards and reagents* - A five decimal place balance (model R200D, Sartorius Corporation, Bohemia, NY)

6. *Top-Loading Balance for tissue samples* - A balance with a minimum of 2 decimal places (model MC1 LC 620S, Sartorius Corporation, Bohemia, NY)

7. *Centrifuge* - Capable of spinning 50 mL tubes at 39800 *g* (Induction Drive Centrifuge, model J2-21M, Beckman Coulter, Fullerton, CA)

8. *Centrifuge tube* - 50 mL tube with screw cap (Polysulfone, Nalge Co., Rochester, NY)

9. *Mechanical shaker* - Wrist action shaker (Shaker model 3589, Lab-Line Instruments, Inc., Melrose Park, IL)

10. *SPE manifold* - Model Baker SPE-24G (J.T. Baker, Phillipsburg, NJ)

11. *Filtration column* - 25 mL, 20 mm i.d. (Lida, Kenosha, WI)

12. *SPE column* - Phenyl, 6 mL, 1000 mg (YMC, Wilmington, NC or AccuBOND by J&W Scientific, Folsom, CA).
    Critical Point: Equivalent columns must give recoveries of 80-120% with %RSD ≤ 20 when a minimum of 7 fortified control replicate samples near the tolerance level are analyzed following this SOP.

13. *Frit* - Polyethylene, 20 mm, porosity 20 µm (Lida, Kenosha, WI)

14. *Vacuum pump* - Capable of filtering and degassing solvents (model DOA-102-AA, Gast Manufacturing Corp., Benton Harbor, MI)

15. *HPLC solvent filters* - 0.45 µm nylon membrane filter for aqueous solvent and 0.2 µm FP vericel membrane filter for organic solvent (Gelman, Ann Arbor, MI)

16. *Analytical evaporator* - Capable of evaporating sample solution with stream of nitrogen (model 8125 nitrogen evaporator, Organomation, Berlin, MA)

17. *HPLC sample filter* - Acrodisc 25 mm, LC PVDF, 0.45 µm (Gelman, Ann Arbor, MI)

18. *HPLC sample vials* - 1.5 mL with open top cap and 8 mm TFE/silicon septum (Sun International Trading, Ltd., Wilmington, NC)

B. Reagents (Equivalent reagents may be used where appropriate)

1. *Acetonitrile* - CAS # 75-05-8, CH_3CN, FW 41.05, HPLC grade (Fisher Scientific, Itasca, IL)

2. *Water* - CAS # 7732-18-5, H_2O, FW 18.02, HPLC grade or Type 1 reagent grade water with an electrical resistance greater than 14.0 megohm/cm

(UMESC, La Crosse, WI)

3. *Oxytetracycline HCl* - CAS # 2058-46-0, $C_{22}H_{24}N_2O_9 \cdot HCl$, FW 496.9, > 95% assay purity (Sigma Chemical, St. Louis, MO)

4. *Ethylenediaminetetraacetic acid, disodium salt dihydrate (EDTA)* - CAS # 6381-92-6, $Na_2C_{10}H_{14}O_8N_2 \cdot 2H_20$, FW 372.24, certified ACS, 99.0-101.0% assay purity range (Fisher Scientific, Itasca, IL)

5. *Citric acid monohydrate* - CAS # 5949-29-1, $C_6H_8O_7 \cdot H_2O$, FW 210.4, certified ACS, 99.0-102.0% assay purity range (Fisher Scientific, Itasca, IL)

6. *Sodium phosphate, dibasic heptahydrate* - CAS # 7782-85-6, $Na_2HPO_4 \cdot 7H_2O$, FW 268.07, ACS reagent, 98.0-102.0% assay purity range (Fisher Scientific, Itasca, IL)

7. *Oxalic acid, dihydrate* - CAS # 6153-56-6, $C_2H_2O_4 \cdot 2H_2O$, FW 126.1, 99.5-102.5% assay purity range (Sigma Chemical, St. Louis, MO)

8. *1-Octanesulfonic acid sodium salt* - CAS # 5324-84-5, $C_8H_{17}O_3SNa$, FW 216.3, approximately 98% pure (Sigma Chemical, St. Louis, MO)

9. *Helium compressed gas* - CAS # 7440-59-7, He, FW 4.0, zero grade (Airgas, La Crosse, WI)

10. *Nitrogen compressed gas* - CAS # 7727-37-9, N_2, FW 28.01, high purity grade (Airgas, La Crosse, WI)

11. *Sylon CT (5% dimethyldichlorosilane in toluene)* - CAS # 75-78-5 (Supelco Inc., Bellefonte, PA)

12. *Trichloroacetic acid solution (TCA)* - CAS # 76-03-9, $C_2HCl_3O_2$, FW 163.4, 6.1 N, 100% w/v (Fisher Scientific, Itasca, IL)

C. Preparation and Storage of Reagents and Solutions (Stability of solutions beyond conditions stated is unknown and can affect the results. Other amounts of reagents or solutions may be made when appropriate.)

1. *McIlvane/EDTA Extraction Buffer (McI/EDTA)*

   a. Dissolve 25.861 g of citric acid monohydrate and 41.243 g of

sodium phosphate dibasic heptahydrate inside a 2-L volumetric flask with water. Adjust to volume with water and mix thoroughly.

b. Add 49.996 g EDTA to the flask and mix thoroughly on a stir plate until dissolved.

c. Storage: ≤ 2 weeks at ambient temperature and lighting[6]

2. *2.5% EDTA rinsing solution (w/v)*

a. Dissolve 25 g EDTA in a 1-L volumetric flask with water. Adjust to volume with water and mix thoroughly.

b. Storage: ≤ 2 weeks at ambient temperature and lighting[6]

3. *20% trichloroacetic acid (TCA) solution*

a. Thoroughly mix 20 mL of 6.1 N TCA and 80 mL of water using graduated cylinders.

b. Storage: ≤ 2 weeks at ambient temperature and lighting[6]

4. *0.3 M Oxalic Acid (elution solution)*

a. Dissolve 37.8 g of oxalic acid in acetonitrile inside a 1-L volumetric flask. Adjust to volume with acetonitrile and mix thoroughly.

b. Storage: ≤ 2 weeks at ambient temperature and lighting[6]

5. *HPLC Mobile Phase*

a. HPLC buffer - Prepare 0.010 M oxalic acid and 0.030 M 1-octanesulfonic acid sodium salt solution by dissolving 2.522 g of oxalic acid and 12.978 g 1-octanesulfonic acid sodium salt with water in a 2-L volumetric flask. Adjust to volume with water and mix thoroughly. Filter and degas the solution with a 47 mm Gelman nylon filter (45 µm pore size) with a vacuum pump.

b. Organic phase - HPLC grade acetonitrile, pass through a Gelman FP vericel membrane filter with a vacuum pump to filter and degas if needed.

c. Mobile phase - An isocratic mobile phase of Buffer/Acetonitrile (70:30) is used to elute oxytetracycline from the extract of fish fillet tissue. The presence of relatively small endogenous interfering peaks in the fillet tissue of some species of fish may require a slight adjustment in the percentages of mobile phases. Sparge HPLC solvents with helium to degas solutions during use if needed.

d. Storage: ≤ 2 weeks at ambient temperature and lighting[6]

D. Standards/Standard Curves (Use of other standard concentrations is acceptable).

1. *Stock and HPLC calibration standards* - Prepare a 1.0 mg/mL OTC free base stock solution by dissolving 25 mg OTC free base (equivalent to 26.98 mg OTC HCl) with HPLC mobile phase (*Procedure: C.5.c*) in a 25-mL volumetric flask. Adjust to volume with mobile phase and mix thoroughly. Working standard solutions of various concentrations are then prepared by volumetrically pipetting the 1.0 mg/mL stock solution, or working standard solutions, into volumetric flasks that are brought to volume with HPLC mobile phase. Calibration standards must bracket the sample concentration and stay within the linearity of the HPLC method.

2. *Standard dilution scheme example* - Transfer an appropriate volume (*Transfer Volume*) from a previously made standard (*Standard Used*) into an appropriate class A volumetric flask (*Final Volume*). Fill the flask to volume with the diluent and mix thoroughly.

Standard Used (µg/mL)	Transfer Volume (mL)	Final Volume (mL)	Final Concentration (µg/mL)
1000	5	100	50
50	1	10	5
50	3	50	3
50	1	25	2
50	1	50	1
50	1	100	0.5

3. *Storage Stability* - ≤ 2 weeks at ambient temperature and lighting[5]

E. Sample Collection

1. Fillet sample representative of the edible portion of the fish should be collected following the appropriate SOPs on sampling and dissecting fish. Immediately use the fillet tissue sample or store at < -70 °C.

2. Homogenize fillet tissue with dry ice as described in SOP No. CAP 402.

F. Sample Storage

Homogenized or unhomogenized samples can be stored frozen (< -70 °C) for at least 2 months[5,6]. Stability of samples beyond conditions stated is unknown and can affect the results.

G. Sample Preparation - One analyst can extract 26 samples in an 8-hour period.
Critical Point: The extraction procedure should be completed in a single day, with no breaks longer than 30 minutes and the SPE clean-up portion conducted as one continuous process.

1. Weigh 5.0 ± 0.1 g of homogenized edible tissue sample into a tared, EDTA-rinsed 50-mL centrifuge tube.

2. Preparation of fortified controls - These samples must be prepared during every analysis to determine accuracy and precision of the analytical procedure for the analysis set. Spike the control sample (minimum of 3 replicates) with an appropriate amount(≤100 µL) of OTC standard. The 50 µg/mL OTC free base standard (*Procedure: D.2*) may be used as an appropriate spiking solution. Allow a minimum contact time of 15 minutes between the fortification solution and the sample matrix before proceeding with step 3 below.

3. Preparation of procedural Standards - These samples should be prepared during every analysis to determine accuracy and precision of the fortification procedure for the analysis set. Concurrently with the spiking of the controls, spike a 5-mL volumetric flask (minimum of 3 replicates) using the same spiking solution, volume, and syringe used for fortifying the control sample. Bring the flask to volume with the mobile phase solution (*Procedure: C.5.c*) and mix thoroughly.

4. Add 8 mL of McI/EDTA to the sample. Since a high degree of accuracy is not required, the McI/EDTA may be added using a graduated cylinder,

pipettor, or similar apparatus.

5. Homogenize on a VirTishear equipped with an open blade assembly for one minute (bend both ends of the blade down at a 90° angle to allow lowering the blade into the centrifuge tube). After homogenizing, rinse any tissue residue off of the blade and shaft into the centrifuge tube with approximately 2 mL of the McI/EDTA solution. Use a clean shaft and blade for each sample. The blade and shaft may be cleaned with a brush under running water. Rinse the shaft and blade in methanol, then deionized water and dry before use.

6. Shake the sample on mechanical shaker for one minute at approximately 90% of maximum. Vortexing of the sample for the same length of time at approximately the same settings works equally well.

7. Centrifuge the sample at a relative centrifugal force (RCF) of 39800, at ambient temperature, for 10 minutes.

8. Decant supernatant into a second EDTA-rinsed 50 mL centrifuge tube.

9. Add 8 mL McI/EDTA to the centrifuge tube containing homogenate and break up pellet with a polypropylene stir rod. Rinse stir rod with approximately 2 mL of the McI/EDTA into the centrifuge tube. Shake, centrifuge and decant as described in steps *Procedure: G.6-8*. Repeat step 7 once more for a total of three extractions.

10. Add 3 mL of 20% TCA (measured with a graduated cylinder or pipettor) to the centrifuge tube containing the combined supernatant. Shake and centrifuge as described in steps *Procedure: G.6-7*.

11. Set up a solid phase extraction (SPE) apparatus as follows (Figure 1):

Figure 1: SPE configuration

a. In a hood, attach a vacuum pump to a solvent trap that is attached to a SPE manifold. Attach stopcocks onto an appropriate number of outlets. Connect a 6 mL, 1000 mg phenyl SPE column to each stopcock. Equip manifold

outlets with inert needle inserts. Place waste containers under each needle in the manifold. Empty containers when necessary to prevent overflow.

b. Apply ~1 mL of Sylon to the phenyl SPE column and allow it to saturate the column bed for 5 minutes. Pass the Sylon through the SPE column and into the waste collection container. On top of the phenyl SPE column, connect in succession an adapter, a stopcock and a 25mL filtration column equipped with one polyethylene frit. Condition the column set-up with ~ 12 mL acetonitrile, followed by ~ 12 mL McI/ EDTA solution, without allowing column to dry. Leave ~ 1 cm McI/ EDTA solution on top of column bed of both the filtration and phenyl columns.

Critical Point: If the phenyl column bed becomes dry at any point before the supernatant is applied, the entire conditioning sequence must be repeated.

12. Carefully pour the combined supernatant from step *Procedure: G.10* into the 20 mL filtration column.

13. Open the stopcock below the reservoir and allow the supernatant to pass into the phenyl column. Open the stopcock below the phenyl column and turn on the vacuum pump.

Critical Point: Maintain an adequate flow of supernatant by adjusting the two stopcocks so that the column does not dry or overflow. Leave about one cm of liquid on the top of the filter and column bed. Flow rate through columns should be ≤ 2 mL/min.

14. Add 8 mL McI/EDTA solution to the centrifuge tube containing the precipitated protein pellet (measured with a graduated cylinder or pipettor) and break up with a polypropylene stir rod. Rinse stir rod with ~2 mL McI/EDTA solution. Shake and centrifuge the samples in the centrifuge tube as described in steps *Procedure: G.6*-7.

15. Pour the supernatant into the filter column, open the stopcock and turn on vacuum to pass the solution through the phenyl SPE column. When the filter reservoir empties, but before the phenyl SPE column dries, add 5 mL of McI/EDTA solution to the reservoir to rinse the filter and pass the solution through the phenyl SPE column. Flow rate through the columns should be ≤ 2 mL/min.

16. After all solutions have passed through the column, dry under vacuum

for ~1 minute (-15 to -20 mm Hg). Remove the waste collection containers and place a labeled 5 mL volumetric flask under each needle insert. Elute oxytetracycline from the phenyl SPE column with five 1000 µL volumes of 0.3 M oxalic acid in acetonitrile using a flow rate of ≤ 2 mL/min.

17. Remove the flasks from the SPE manifold and place them on a nitrogen evaporator. Evaporate the samples with a stream of nitrogen to near dryness at a temperature between 20° and 30°C. Bring the flask to volume with LC mobile phase and dissolve the residue by inverting the stoppered flask.

Critical Point: "Near dryness" means less than 0.5 mL, but not completely dry. If not enough acetonitrile is evaporated, the analyte peak shape of the resulting chromatogram will be affected adversely. If allowed to dry completely, recovery may be compromised due to possible difficulty in re-dissolving content in mobile phase.

18. Filter approximately 1.0 to 1.5 mL of each sample into a properly labeled HPLC vial, by passing it through a 25 mm, LC PVDF (0.45 µm) filter with a one cc syringe.

Note: Extract samples are stable in sample vials for at least one week stored at ambient temperature and lighting[5]. Stability of samples beyond conditions stated is unknown and can affect the results.

H. Instrument Preparation

1. The analyst must refer to the appropriate HPLC instrument operating procedures for instructions on setting up the HPLC.

2. The HPLC operating conditions are as follows:

HPLC column:	YMC, C_{18}, 5 µm, 250 x 4.6 mm ID
Mobile phase:	70:30 buffer/acetonitrile, isocratic (see *C.5*)
Flow rate:	1.0 mL/minute
Column temp:	45 °C
Injection:	100 µL
Detection:	UV at 355 nm
Retention time:	Between 9 - 10 minutes
Run time:	12 minutes

Other operating conditions may be used according to the specifications of alternative instrumentation and/or laboratory variables. When using alternative HPLC operating conditions, they must produce similar system

performance (See section J below). They must also satisfactorily separate the analyte from the matrix interferences.

I. Sample Analysis

1. The analyst must refer to the appropriate HPLC instrument operating procedures for instructions on operating the HPLC.

2. The chemical species separated and analyzed by the HPLC system is OTC free base. Process the samples on the HPLC using the above operating conditions (*Procedure: H.2*) along with the following:

   a. A minimum four-point calibration curve encompassing the expected sample concentration

   b. A minimum of three replicates of a quality control standard

   c. A minimum of three fortified controls

   d. A minimum of three procedural standards (optional)

3. The analyst must refer to the HPLC SOP for appropriate data analysis and reduction methods.

J. System Suitability

1. System suitability requirements for this method may vary from one study to another. The suitability parameters used should be included with the results of analyses.

2. The following system suitability parameters and acceptance criteria were used when developing this method:

Suitability parameters	**Acceptance Criteria**
Precision of Quality Control Standard	%RSD ≤ 5
Accuracy and Precision of Procedural Standards	Mean Concentration within 10% theoretical %RSD ≤ 5
Accuracy and Precision of Fortified Samples	Recovery between 80 to 120% %RSD ≤ 20
Coefficient of correlation (r) or determination (r^2) of daily calibration curve	$r \geq 0.995$ or $r^2 \geq 0.99$
Empirical OTC standard concentration	Concentration within 10% theoretical

Retention time (t_R) of OTC standards	Individual t_R within 5% of mean value
Empirical sample results	Pass Q-test (Note: In order for a sample to be excluded from calculations or rejected, it must fail the Q-test or have documented evidence that the analysis was not conducted properly.

K. Calculations

1. Sample Concentration - The tolerance of OTC in fish tissue (2 ppm) is reported as the free base (21CFR556.500). The concentration of OTC in edible fish tissue will be expressed in µg/g OTC free base. When injections of samples and calibration standards are of equal volume, OTC concentration is calculated using the following equation:

   A = BC/D

   where,

   A = OTC free base concentration in the edible tissue (µg/g)
   B = OTC free base concentration in the final extract sample (µg/mL)
   C = Final extract sample volume (5 mL)
   D = Mass of sample (5 ± 0.1 g)

2. Percent recovery of fortified control sample:

$$\%\,\text{Recovery} = \frac{\text{Recovered Concentration}\,(\mu g/g)}{\text{Theoretical Concentration}\,(\mu g/g)} \times 100$$

3. Statistical Q-Test[7] - The Q-test is a simple statistical test to determine if a data point that appears to be very different from the rest of the data points in a set may be discarded. Only one data point in a set may be rejected using this test.

$$Q = \frac{(\text{suspected outlier} - \text{closest value})}{(\text{largest value} - \text{smallest value})}$$

   If $Q > Q_{96}$, the outlier can be discarded with 96% confidence.

Q Critical Values (96% Confidence)	
N	Q_{96}
3	0.98
4	0.85
5	0.73
6	0.64
7	0.59
8	0.54
9	0.51
10	0.48

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