

BRIEFING

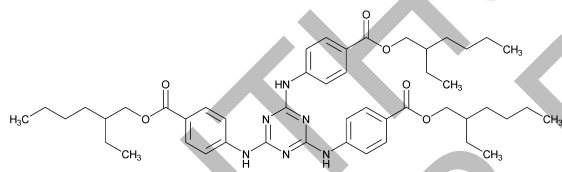
Ethylhexyl Triazone. This monograph was posted on the USP Website as a draft USP Pending Standard for public comment. No comments were received. The MD-ODD Expert Committee reviewed the draft and approved the monograph as an Authorized USP Pending Standard. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the WAKO Pure Chem FluoFix column. The typical retention times reported for ethylhexyl triazone related compounds A, B, and C and ethylhexyl triazone are about 4, 5.5, 7.5, and 13 minutes, respectively. The gas chromatographic procedure in the test for *Limit of 2-ethylhexan-1-ol* is based on analysis performed with the Chrompack CP-Wax 52 CB brand of G16 column. The typical retention time reported for 2-ethylhexan-1-ol is about 31 minutes.

(MD-ODD: F. Mao) RTS—C44123

Add the following:

■ **Ethylhexyl Triazone**

v. 1 Authorized September 20, 2007



$C_{48}H_{66}N_6O_6$ 823.07

2-Ethylhexyl 4-[[[4,6-bis[[4-(2-ethylhexoxycarbonyl)phenyl]amino]-1,3,5-triazin-2-yl]amino]benzoate.

Tris(2-ethylhexyl) 4,4',4''-(1,3,5-triazine-2,4,6-triyl)tris(azanediyl)tribenzoate [88122-99-0].

» Ethylhexyl Triazone contains not less than 97.5 percent and not more than 102.0 percent of $C_{48}H_{66}N_6O_6$, calculated on the anhydrous and solvent-free basis.

Packaging and storage—Preserve in tight containers. Store at room temperature.

USP Reference standards <11>—*USP 2-Ethylhexan-1-ol RS*. *USP Ethylhexyl Triazone RS*. *USP Ethylhexyl Triazone Related Compound A RS*. *USP Ethylhexyl Triazone Related Compound B RS*. *USP Ethylhexyl Triazone Related Compound C RS*.

Identification—

A: *Infrared Absorption* <197K>.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Melting temperature, Class Ia (741): not higher than 132°.

Water, Method I (921): not more than 0.5%.

Heavy metals, Method II (231): not more than 10 ppm.

Clarity in medium-chain triglycerides—

Test solution—Transfer 96.0 g of medium-chain triglycerides into a 150-mL Erlenmeyer flask and heat to 40°. While stirring, slowly add 4.0 g of Ethylhexyl Triazone. Stir the resulting yellowish suspension for about 6 hours at 40°, and allow to stand for 12 hours at room temperature. Stir the suspension again for 10 minutes at room temperature.

Procedure—Measure the *Test solution* at 860 nm in a 20-mm round cell: the turbidity is not more than 3 nephelometric turbidity units (NTU) (see *Spectrophotometry and Light Scattering* <851>).

Limit of halogens (calculated as chlorine)—

Electrolyte solution—Prepare a mixture of water and acetic acid (4:3).

Apparatus—Use a coulometric chlorine analyzer, and set the combustion temperature and flow rates of the reaction gas and the carrier gas according to the instrument manual.

Procedure—Transfer about 10 mg of Ethylhexyl Triazone, accurately weighed, into a quartz boat. The sample is introduced into the combustion kiln by means of an automatic slide-in module. The combustion gases produced pass through sulfuric acid to dry and then arrive in the coulometer

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cell filled with *Electrolyte solution*. [NOTE—Before each fresh charge of *Electrolyte solution*, add approximately 50 mg of hydrazine sulfate to the measuring cell.] Measure the electric charge produced and calculate the percentage of chlorine in the portion of Ethylhexyl Triazone taken by the formula:

$$100(M \times m)/(F_c \times W)$$

in which M is the measured electric charge, in mC; m is the molar mass of chlorine, 3.5453×10^4 mg per mol; F_c is the Faraday constant, 96.487×10^6 mC/mol; and W is the weight, in mg, of ethylhexyl triazone: not more than 0.005% of halogens, calculated as chlorine, is found.

Limit of iron—

Standard solution—Dilute quantitatively, and stepwise if necessary, a commercially available iron atomic absorption standard solution containing about 1.000 g of iron per L with 0.2 N nitric acid to obtain a solution having a known concentration of about 0.8 μ g per mL.

Test solution—Weigh accurately 1 to 2 g of Ethylhexyl Triazone in a crucible. Moisten the sample with about 1 mL of sulfuric acid, then heat gently at a temperature as low as practicable until the sample is thoroughly charred. Cool, then moisten the residue with about 1 mL of sulfuric acid, heat gently until white fumes are no longer evolved, and ignite at $600 \pm 50^\circ$ until the residue is completely incinerated. Ensure that flames are not produced at any time during the procedure. Cool the crucible in a desiccator (silica gel or other suitable desiccant). Dissolve the residue obtained in 20 mL of 2 N nitric acid. Slowly evaporate this solution to approximately 5 mL, transfer to a 25-mL volumetric flask, and dilute with 0.2 N nitric acid to volume.

Procedure—Concomitantly determine the absorbances of the *Standard solution* and the *Test solution* at 248 nm with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* (851)) equipped with an

iron hollow-cathode lamp and an air-acetylene flame, using water as the blank: the absorbance of the *Test solution* is not more than that of the *Standard solution*.

Limit of 2-ethylhexan-1-ol—

Standard solution—Dissolve, stepwise if necessary, an accurately weighed quantity of USP 2-Ethylhexan-1-ol RS in *N,N*-dimethylacetamide to obtain a solution having a known concentration of about 0.1 mg per mL. Transfer 1.0 mL of this solution into an appropriate headspace vial containing 1.0 g of Ethylhexyl Triazone, add 50 μ L of water, close the vial, and mix thoroughly.

Resolution solution—Dissolve suitable quantities of ethyl benzene and *p*-xylene in *N,N*-dimethylacetamide to obtain a solution having known concentrations of about 0.2 mg per mL of each. Transfer 0.1 mL of this solution into an appropriate headspace vial, add 0.9 mL of *N,N*-dimethylacetamide and 50 μ L of water, close the vial, and mix thoroughly.

Test solution—Transfer 1.0 g of Ethylhexyl Triazone, accurately weighed, into an appropriate headspace vial, dissolve in 1.0 mL of *N,N*-dimethylacetamide, add 50 μ L of water, close the vial, and mix thoroughly.

Chromatographic system (see *Chromatography* (621))—The gas chromatograph is equipped with a headspace injector, a flame-ionization detector, and a split injection system with a split ratio of about 5:1. It contains a 0.32-mm \times 50-m fused-silica capillary column coated with a 1.2- μ m film of phase G16. The carrier gas is helium, flowing at a constant column head pressure of 0.9 bar (corresponds to 1.8 mL per minute at 50°). The chromatograph is programmed as follows: the temperature of the column is maintained at 50° for 5 minutes, then the temperature is increased at a rate of 5° per minute to 200° and maintained at the 200° for 15 minutes; the vial is heated to 90° for 60 minutes, the transfer line is heated to 150° , and the injection port and the detector block are maintained at a temperature of 250° . Chromatograph the *Resolution solution*, and record the peak areas as directed for *Procedure*: the resolution, R , between ethyl benzene and *p*-xylene is not less than 1.5. Chromatograph the *Standard*

solution, and record the peak areas as directed for *Procedure*: the relative standard deviation of the 2-ethyl hexanol peak for replicate injections is not more than 10%.

Procedure—Separately inject equal volumes (about 1.0 mL) of the headspace of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentages of 2-ethylhexan-1-ol in the portion of Ethylhexyl Triazone taken by the formula:

$$100(C/W)[r_v / (r_s - r_v)]$$

in which *C* is the concentration, in mg per mL, of USP 2-Ethylhexan-1-ol RS in the *Standard solution*; *W* is the weight, in mg, of Ethylhexyl Triazone taken to prepare the *Test solution*; *r_v* is the peak area of 2-ethylhexan-1-ol obtained from the *Test solution*; and *r_s* is the peak area of 2-ethylhexan-1-ol obtained from the *Standard solution*: not more than 0.02% of 2-ethylhexan-1-ol is found.

Related compounds—

Mobile phase and *System suitability solution*—Proceed as directed in the *Assay*.

Standard solution—Dissolve an accurately weighed quantity of USP Ethylhexyl Triazone RS in a minimum amount of tetrahydrofuran, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.001 mg per mL.

Test solution—Dissolve an accurately weighed quantity of Ethylhexyl Triazone in a minimum amount of tetrahydrofuran, and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 1.0 mg per mL.

Chromatographic system (see *Chromatography* (621))—Prepare as directed in the *Assay* except for chromatographing the *Standard preparation*. Chromatograph the *Standard solution*, and record the peak areas as directed for *Procedure*: the relative standard deviation of the ethylhexyl triazone peak for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into a chromatograph, and allow the chromatogram to run for 25 minutes. Record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Ethylhexyl Triazone taken by the formula:

$$100(1/F)(C_s / C_v)(r_i / r_s)$$

in which *F* is the relative response factor for each impurity, obtained from *Table 1*; *C_s* is the concentration, in mg per mL, of USP Ethylhexyl Triazone RS in the *Standard solution*; *C_v* is the concentration, in mg per mL, of Ethylhexyl Triazone in the *Test solution*; *r_i* is the peak area for each impurity obtained from the *Test solution*; and *r_s* is the peak area for ethylhexyl triazone obtained from the *Standard solution*. [NOTE—Disregard any peak with an area of less than 0.5 times the area of the ethylhexyl triazone peak in the *Standard solution*.] The limits are given in *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor (<i>F</i>)	Limit (%)
Ethylhexyl triazone	0.32	0.89	NMT 0.2
related compound A ¹			
Ethylhexyl triazone	0.44	1.15	NMT 0.2
related compound B ²			
Ethylhexyl triazone	0.58	1.12	NMT 0.2
related compound C ³			
Ethylhexyl triazone	1.00	1.00	—
Individual unspecified impurity	—	1.00	NMT 0.1
Total impurities	—	—	NMT 0.8

¹ 2-Ethylhexyl 4-aminobenzoate [C₁₅H₂₃NO₂, 249.35].

² 4-(4,6-Bis(4-((2-ethylhexyloxy)carbonyl)phenylamino)-1,3,5-triazin-2-ylamino)benzoic acid [C₄₀H₅₀N₆O₆, 710.86].

³ Bis(2-ethylhexyl) 4,4'-(6-(4-(ethoxycarbonyl)phenylamino)-1,3,5-triazine-2,4-diyl)bis(azanediyl)dibenzoate [C₄₂H₅₄N₆O₆, 738.91].

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Assay—

Mobile phase—Prepare a mixture of tetrahydrofuran, acetonitrile, and water (38:34:28). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

Standard preparation—Dissolve an accurately weighed quantity of USP Ethylhexyl Triazone RS in a minimum amount of tetrahydrofuran, and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

System suitability solution—Dissolve suitable quantities of USP Ethylhexyl Triazone RS, USP Ethylhexyl Triazone Related Compound A RS, USP Ethylhexyl Triazone Related Compound B RS, and USP Ethylhexyl Triazone Related Compound C RS in a minimum amount of tetrahydrofuran, and dilute, stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations about 0.01 mg per mL of each.

Assay preparation—Dissolve an accurately weighed quantity of Ethylhexyl Triazone in a minimum amount of tetrahydrofuran, and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 295-nm detector and a 4.6-mm × 25-cm column that contains

5- μ m packing L##. The flow rate is about 1 mL per minute. The column temperature is maintained at 30°. Chromatograph the *System suitability solution*, and record the peak areas as directed for *Procedure*: the resolution, *R*, between ethylhexyl triazone related compound A and ethylhexyl triazone related compound B is not less than 5.0. Chromatograph the *Standard preparation*, and record the peak areas as directed for *Procedure*: the relative standard deviation of the ethylhexyl triazone peak for replicate injections is not more than 2.0%. [NOTE—Before using a new column, equilibration using methanol at 1 mL per minute for 3 hours is required.]

Procedure—Inject equal volumes (about 10 μ L) of the *Standard preparation* and the *Assay preparation* into a chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of C₄₈H₆₆N₆O₆ in the portion of Ethylhexyl Triazone taken by the formula:

$$100(C_s/C_u)(r_u/r_s)$$

in which *C_s* is the concentration, in mg per mL, of USP Ethylhexyl Triazone RS in the *Standard preparation*; *C_u* is the concentration, in mg per mL, of Ethylhexyl Triazone in the *Assay preparation*; and *r_u* and *r_s* are the peak areas obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■