⟨228⟩ ETHYLENE OXIDE AND DIOXANE

The following procedure is used to determine the contents of residual ethylene oxide and dioxane in the products prepared from ethylene oxide. Unless otherwise directed in the individual monograph, use *Method I*.

Method I

[**CAUTION**—Ethylene oxide is toxic and flammable. Prepare these solutions in a well-ventilated fume hood, using great care. Protect both hands and face by wearing polyethylene protective gloves and an appropriate face mask. Store all solutions in hermetic containers, and refrigerate between 4° and 8°.]

[NOTE—Before using the polyethylene glycol 200 in this test, remove any volatile components from it by placing 500 mL of polyethylene glycol 200 in a 1000-mL round-bottom flask and attaching the flask to a rotary evaporator maintained at 60° and under a vacuum of 10–20 mm Hg for 6 h.]

Acetaldehyde solution: 10 µg/mL of acetaldehyde. [NOTE—Prepare immediately before use.]

Ethylene oxide stock solution: 2.5 mg/g of ethylene oxide.

Prepare as follows: Tare a glass-stoppered conical flask, add 50 mL of polyethylene glycol 200, and reweigh the flask. Transfer 5 mL of the liquid ethylene oxide to a 100-mL beaker chilled in a mixture of sodium chloride and ice (1:3). Transfer 300 µL (corresponding to 250 mg) of liquid ethylene oxide to the polyethylene glycol 200, and swirl gently to mix. Replace the stopper, reweigh the flask, and determine the amount of ethylene oxide absorbed by weight difference. Adjust the weight of the mixture with polyethylene glycol 200 to 100.0 g, replace the stopper, and swirl gently to mix. [NOTE—Fill a chilled pressure bottle with liquid ethylene oxide, and store in a freezer when not in use. Use a small piece of polyethylene film to protect the liquid from contact with the rubber gasket. Use an adequately chilled apparatus where appropriate. Prepare this stock solution immediately prior to use, and store in a refrigerator after preparation.]

Ethylene oxide solution: Tare a glass-stoppered conical flask, and chill it in a refrigerator. Add 35 mL of polyethylene glycol 200, and reweigh the flask. Transfer 1 g of chilled *Ethylene oxide stock solution* to the tared conical flask. Adjust the weight of the solution with polyethylene glycol 200 to 50.0 g, replace the stopper, and swirl gently to mix. Transfer 10 g of this solution to a 50-mL volumetric flask. Add 30 mL of water, and mix. Dilute with water to volume, and mix to obtain a solution containing 10 µg/mL of ethylene oxide. [NOTE—Use an adequately chilled apparatus where appropriate. Prepare immediately before use.]

Dioxane solution: 500 µg/mL of dioxane

Standard solution A: Transfer 0.1 mL of *Ethylene oxide solution* to a 10-mL pressure headspace vial. [NOTE—Other sizes such as a 22-mL pressure headspace vial may be used, depending on operating conditions; however, the same size must be used for *Standard solution A*, *Standard solution B*, and the *Sample solution*.] Add 0.1 mL of *Acetaldehyde solution* and 0.1 mL of *Dioxane solution*, seal the vial, and mix.

Standard solution B: Transfer 1.0 g of the test substance to a 10-mL pressure headspace vial, and add 0.1 mL of *Ethylene oxide solution*, 0.1 mL of *Dioxane solution*, and 1.0 mL of *N*,*N*-dimethylacetamide. Seal the vial, and mix.

Sample solution: Transfer 1.0 g of the test substance to a 10-mL pressure headspace vial, and add 1.0 mL of *N*,*N*-dimethylacetamide and 0.2 mL of water. Seal the vial, and mix.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: Headspace GC

Detector: Flame ionization

Column: 0.32-mm × 30-m glass or quartz capillary; 1.0-µm layer of phase G1

Temperature

Injector port: 150°

Detector: 250°

Column: See the column temperature table below.

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	—	50	5
50	5	180	—
180	30	230	5

Carrier gas: Helium

Linear velocity: 20 cm/s

Injection volume: 1 mL (gaseous headspace)

Injection type: Split ratio 20:1

Headspace sampler

Temperature equilibration time: 45 min

Equilibration temperature

70° for *Standard solution A*

90° for *Standard solution B*

90° for *Sample solution*

Transfer line temperature: 150°

Pressurization time: 1 min

Injection time: 12 s

System suitability
Sample: *Standard solution A*
[NOTE—The relative retention times for acetaldehyde and ethylene oxide are 0.94 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.0 between acetaldehyde and ethylene oxide
Signal-to-noise ratio: NLT 5, determined from the dioxane peak
Relative standard deviation: NMT 15%
Analysis
Samples: *Standard solution B* and *Sample solution*
[NOTE—The relative retention times for ethylene oxide and dioxane are 1.0 and 2.5, respectively.]
Calculate the content of ethylene oxide, in ppm, in the portion of the test substance taken:

$$\text{Result} = A_E \times r_U/[(r_S \times W_U) - (r_U \times W_S)]$$

A_E = quantity of ethylene oxide added to *Standard solution B* (µg)
r_U = ethylene oxide peak responses from the *Sample solution*
r_S = ethylene oxide peak responses from *Standard solution B*
W_U = weight of the test substance taken to prepare the *Sample solution* (g)
W_S = weight of the test substance taken to prepare *Standard solution B* (g)

Calculate the content of dioxane, in ppm, in the portion of the test substance taken:

$$\text{Result} = A_D \times r_U/[(r_S \times W_U) - (r_U \times W_S)]$$

A_D = quantity of dioxane added to *Standard solution B* (µg)
r_U = dioxane peak responses from the *Sample solution*
r_S = dioxane peak responses from *Standard solution B*
W_U = weight of the test substance taken to prepare the *Sample solution* (g)
W_S = weight of the test substance taken to prepare *Standard solution B* (g)

Method II

Ethylene oxide standard solution: Dilute 0.5 mL of ethylene oxide in methylene chloride (50 mg/mL)[1] with water to 50.0 mL. [NOTE—The solution is stable for 3 months if stored in vials with polytetrafluoroethylene (polytef)-coated silicon membrane crimped caps at –20°.] Allow to reach room temperature. Dilute 1.0 mL with water to 250.0 mL to obtain a solution having a concentration of 2 µg/mL of ethylene oxide. [NOTE—Use this solution immediately after preparation.]
Dioxane standard solution: 0.05 µL/mL of dioxane
Acetaldehyde standard solution: 10 µg/mL of acetaldehyde. [NOTE—Prepare immediately before use.]
Resolution solution: Add 2.0 mL of *Acetaldehyde standard solution* and 2.0 mL of *Ethylene oxide standard solution* to a 10-mL headspace vial. Seal the vial immediately with a polytef-coated silicon membrane and an aluminum cap, and mix carefully.
Standard solution A: 0.48 µg/mL of ethylene oxide, from *Ethylene oxide standard solution*, and 0.005 µL/mL of dioxane, from *Dioxane standard solution*, in water
Standard solution B: Transfer 1.0 g of the test substance into a 10-mL headspace vial. Add 2.0 mL of *Standard solution A*, seal the vial immediately with a polytef-coated silicon membrane and an aluminum cap, and mix carefully.
Sample solution: Transfer 1.0 g of the test substance into a 10-mL headspace vial. Add 2.0 mL of water, seal the vial immediately with a polytef-coated silicon membrane and an aluminum cap, and mix carefully.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: Headspace GC
Detector: Flame ionization
Column: 0.53-mm × 50-m fused-silica capillary column; 5.0-µm layer of phase G27
Temperature
Injector port: 85°
Detector: 250°
Column: See the column temperature table below.

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
70	10	250	5

Carrier gas: Helium
Flow rate: 4 mL/min
Injection volume: 1 mL (gaseous headspace)
Injection type: Split ratio 3.5 : 1
Headspace sampler
Temperature equilibration time: 30 min
Equilibration temperature: 80°

[1] This is a commercially available solution.

System suitability

Sample: *Resolution solution*

[NOTE—The relative retention times for acetaldehyde and ethylene oxide are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between acetaldehyde and ethylene oxide

Analysis

Samples: *Standard solution B* and *Sample solution*

[NOTE—The relative retention times for ethylene oxide and dioxane are 1.0 and 1.9, respectively.]

Calculate the content of ethylene oxide, in ppm, in the portion of the test substance taken:

$$\text{Result} = C_E \times V \times r_U/[(r_S \times W_U) - (r_U \times W_S)]$$

C_E = concentration of ethylene oxide in the *Standard solution A* (µg/mL)
V = volume of *Standard solution A* added to *Standard solution B* (2.0 mL)
r_U = ethylene oxide peak responses from the *Sample solution*
r_S = ethylene oxide peak responses from *Standard solution B*
W_U = weight of the test substance taken to prepare the *Sample solution* (g)
W_S = weight of the test substance taken to prepare *Standard solution B* (g)

Calculate the content of dioxane, in ppm, in the portion of the test substance taken:

$$\text{Result} = C_D \times V \times \rho \times F \times r_U/[(r_S \times W_U) - (r_U \times W_S)]$$

C_D = concentration of dioxane in *Standard solution A* (µL/mL)
V = volume of *Standard solution A* added to *Standard solution B* (2.0 mL)
ρ = density of dioxane (1.03 g/mL = 1.03 mg/µL)
F = conversion factor (1000 µg/mg)
r_U = dioxane peak responses from the *Sample solution*
r_S = dioxane peak responses from *Standard solution B*
W_U = weight of the test substance taken to prepare the *Sample solution* (g)
W_S = weight of the test substance taken to prepare *Standard solution B* (g)