⟨467⟩ RESIDUAL SOLVENTS

(Chapter under this new title—to become official July 1, 2007)
(Current chapter title is** ⟨467⟩ *Organic Volatile Impurities)

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The residual solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance or an excipient may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical element in the synthetic process. This General Chapter does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Because residual solvents do not provide therapeutic benefit, they should be removed, to the extent possible, to meet ingredient and product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Solvents that are known to cause unacceptable toxicities (Class 1, *Table 1*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Solvents associated with less severe toxicity (Class 2, *Table 2*) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, *Table 3*) should be used where practical. The complete list of solvents included in this General Chapter is given in *Appendix 1*. These tables and the list are not exhaustive. Where other solvents have been used, based on approval by the competent regulatory authority, such solvents may be added to the tables and list.

Testing of drug substances, excipients, and drug products for residual solvents should be performed when production or purification processes are known to result in the presence of such residual solvents. It is only necessary to test for residual solvents that are used or produced in the manufacture or purification processes.

Although manufacturers may choose to test the drug product, a cumulative procedure may be used to calculate the residual solvent levels in the product from the levels in its ingredients. If the calculation results in a level equal to or below that recommended in this General Chapter, no testing of the drug product for residual solvents needs to be considered. If, however, the calculated levels are above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent levels to within acceptable amounts. A drug product should also be tested if a residual solvent is used during its manufacture.

See *Appendix 2* for additional background information related to residual solvents.

CLASSIFICATION OF RESIDUAL SOLVENTS BY RISK ASSESSMENT

The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and the term "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The term "permitted daily exposure" (PDE) is defined as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADIs of the same substance.

Residual solvents specified in this General Chapter are listed in *Appendix 1* by common names and structures. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class 1	Residual Solvents: Solvents to be Avoided Known human carcinogens Strongly suspected human carcinogens Environmental hazards
Class 2	Residual Solvents: Solvents to be Limited Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.
Class 3	Residual Solvents: Solvents with Low Toxic Potential Solvents with low toxic potential to humans; no health-based exposure limit is needed. [NOTE—Class 3 residual solvents may have PDEs of up to 50 mg or more per day.]*

* For residual solvents with PDEs of more than 50 mg per day, see the discussion in the section *Class 3* under *Limits of Residual Solvents*.

PROCEDURES FOR ESTABLISHING EXPOSURE LIMITS

The procedure used to establish permitted daily exposures for residual solvents is presented in *Appendix 3*.

OPTIONS FOR DETERMINING LEVELS OF CLASS 2 RESIDUAL SOLVENTS

Two options are available to determine levels of Class 2 residual solvents.

Option 1

The concentration limits in ppm stated in *Table 2* are used. They were calculated using equation (1) below by assuming a product weight of 10 g administered daily.

$$\text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}} \quad (1)$$

Here, PDE is given in terms of mg per day, and dose is given in g per day.

These limits are considered acceptable for all drug substances, excipients, and drug products. Therefore, this option may be applied if the daily dose is not known or fixed. If all drug substances and excipients in a formulation meet the limits given in *Option 1,* these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g per day are to be considered under *Option 2.*

Option 2

It is not necessary for each component of the drug product to comply with the limits given in *Option 1.* The PDE in terms of mg per day as stated in *Table 2* can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in a drug product. Such limits are considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum. The limits should be realistic in relation to analytical precision, manufacturing capability, and reasonable variation in the manufacturing process. The limits should also reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product. The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the application of *Option 1* and *Option 2* to acetonitrile concentration in a drug product. The permitted daily exposure to acetonitrile is 4.1 mg per day; thus, the *Option 1* limit is 410 ppm. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	400	0.36
Excipient 2	3.8	800	3.04
Drug product	5.0	728	3.64

Excipient 1 meets the *Option 1* limit, but the drug substance, excipient 2, and drug product do not meet the *Option 1* limit. Nevertheless, the drug product meets the *Option 2* limit of 4.1 mg per day and thus conforms to the acceptance criteria in this General Chapter.

Consider another example using acetonitrile as the residual solvent. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	2000	1.80
Excipient 2	3.8	800	3.04
Drug product	5.0	1016	5.08

In this example, the drug product meets neither the *Option 1* nor the *Option 2* limit. The manufacturer could test the drug product to determine if the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced to the allowed limit during formulation, the product fails the requirements of the test.

LIMITS OF RESIDUAL SOLVENTS

Ethylene Oxide

[NOTE—The test for ethylene oxide is conducted only where specified in the individual monograph.] The standard solution parameters and the procedure for determination are described in the individual monograph. Unless otherwise specified in the individual monograph, the limit is 10 µg per g.

Class 1

Class 1 residual solvents *(Table 1)* should not be employed in the manufacture of drug substances, excipients, and drug products because of the unacceptable toxicities or deleterious environmental effects of these residual solvents. However, if their use in order to produce a medicinal product is unavoidable, their levels should be restricted as shown in *Table 1,* unless otherwise stated in the individual monograph. The solvent 1,1,1-trichloroethane is included in *Table 1* because it is an environmental hazard. The stated limit of 1500 ppm is based on safety data.

When Class 1 residual solvents are used or produced in the manufacture or purification of a drug substance, excipient, or drug product, these solvents should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for evaluation.

Table 1. Class 1 Residual Solvents

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Class 2

Class 2 residual solvents *(Table 2)* should be limited in drug substances, excipients, and drug products because of the inherent toxicities of the residual solvents. PDEs are given to the nearest 0.1 mg per day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of the determination procedure. Precision should be determined as part of the procedure validation.

If Class 2 residual solvents are present at greater than their *Option 1* limits, they should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for evaluation.

[NOTE—The following Class 2 residual solvents are not readily detected by the headspace injection conditions described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter: formamide, 2-ethoxyethanol,*N*-methylpyrrolidone, and sulfolane. Other appropriate validated procedures are to be employed for the quantification of these residual solvents. Such procedures shall be submitted to the USP for review and possible inclusion in the relevant individual monograph.]

Table 2. Class 2 Residual Solvents

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylene chloride	6.0	600
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890

Table 2. Class 2 Residual Solvents *(Continued)*

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Trichloroethylene	0.8	80
Xylene*	21.7	2170

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene

Class 3

Class 3 residual solvents *(Table 3)* may be regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

Unless otherwise stated in the individual monograph, Class 3 residual solvents are limited to not more than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option 1*). If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day, that residual solvent should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for evaluation. USP Reference Standards, where available, should be used in these procedures.

Table 3. Class 3 Residual Solvents
(limited by GMP or other quality-based requirements in drug substances, excipients, and drug products)

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethylketone
tert-Butylmethyl ether	Methylisobutylketone
Cumene	2-Methyl-l-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Other Residual Solvents

The residual solvents listed in *Table 4* may also be of interest to manufacturers of drug substances, excipients, or drug products. However, no adequate toxicological data on which to base a PDE was found.

Table 4. Other Residual Solvents
(for which no adequate toxicological data was found)

1,1-Diethoxypropane	Methyl isopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Solvent hexane
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

IDENTIFICATION, CONTROL, AND QUANTIFICATION OF RESIDUAL SOLVENTS

[NOTE—The organic-free water specified in the following procedures produces no significantly interfering peaks when chromatographed.]

Class 1 and Class 2 Residual Solvents

WATER-SOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100-mL volumetric flask, add 9 mL of dimethyl sulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with water to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution A.* Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture B RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution B.*

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 5.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test Solution—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of *Test Stock Solution,* apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution, Class 1 System Suitability Solution,* and *Class 2 Mixture A Standard Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in the table below) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution,* and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or

either of the two *Class 2 Mixture Standard Solutions,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Table 5. Headspace Operating Parameters

	Headspace Operating Parameter Sets		
	1	2	3
Equilibration temperature (°)	80	105	80
Equilibration time (min.)	60	45	45
Transfer-line temperature (°)	85	110	105
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressurization time (s)	30	30	30
Injection volume (mL)	1	1	1

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 2 Standard Stock Solutions, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Test Stock Solution, Test Solution, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Class 2 System Suitability Solution—Transfer 1.0 mL of USP Residual Solvent Class 2—Acetonitrile RS and 1.0 mL of USP Residual Solvent Class 2—Trichloroethylene RS to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 0.25-µm layer of phase G16, or a 0.53-mm × 30-m wide-bore column coated with a 0.25-µm layer of phase G16. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second and a split ratio of 1 : 5. The column temperature is maintained at 50° for 20 minutes, then raised at a rate of 6° per minute to 165°, and maintained at 165° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution,* the *Class 1 System Suitability Solution,* and the *Class 2 System Suitability Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of benzene in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and trichloroethylene in the *Class 2 System Suitability Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution,* the *Class 2 Mixture A Standard Solution,* the *Class 2 Mixture B Standard Solution,* and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in the *Test Solution* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions,* proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 2 Standard Stock Solution A, Class 2 Mixture A Standard Solution, Test Stock Solution, Test Solution, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Standard Solution—[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Spiked Test Solution—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of the *Standard Solution,* apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—[NOTE—If the results of the chromatography from *Procedure A* are found to be inferior to those found with *Procedure B,* the *Chromatographic System* from *Procedure B* may be substituted.] The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution,* the *Class 1 System Suitability Solution,* and the *Class 2 Mixture A Standard Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution,* the *Test Solution,* and the *Spiked Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$5(C/W)[r_U/(r_{ST} - r_U)]$$

in which C is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and r_{ST} are the peak responses of each residual solvent obtained from the *Test Solution* and the *Spiked Test Solution,* respectively.

WATER-INSOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, Class 2 Standard Stock Solution B, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, and *Chromatographic System*—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*

Class 2 Standard Stock Solution C—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture C RS to a 100-mL volumetric flask, dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix.

Class 2 Mixture C Standard Solution—[NOTE—This solution is used for the identification and quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer 1.0 mL of *Class 2 Standard Stock Solution C* to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with dimethylformamide to volume, and mix.

Test Solution 1—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of dimethylformamide, apply the stopper, cap, and mix.

Test Solution 2—[NOTE—This solution is used for the identification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix.

Transfer 5.0 mL of this solution to an appropriate headspace vial, add 1.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution, Test Solution 1,* and *Test Solution 2* (if applicable) into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak in *Test Solution 1* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or any of the three *Class 2 Mixture Standard Solutions,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test. If the peak response for dimethylformamide or *N,N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2 Mixture C Standard Solution,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, Class 2 Standard Stock Solution B, Class 2 Mixture A Standard Solution, and *Class 2 Mixture B Standard Solution*—Prepare as directed for *Procedure A* under *Water-Soluble Articles.*

Class 2 Standard Stock Solution C, Class 2 Mixture C Standard Solution, Test Stock Solution, Test Solution 1, and *Test Solution 2*—Proceed as directed for *Procedure A.*

Class 2 System Suitability Solution and *Chromatographic System*—Proceed as directed for *Procedure B* under *Water-Soluble Articles.*

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution, Test Solution 1,* and/or *Test Solution 2* (if applicable) into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in *Test Solution 1* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or any of the three *Class 2 Mixture Standard Solutions,* proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test. If the peak response for dimethylformamide or *N,N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2 Mixture Standard Solution, C* proceed to *Procedure C* to quantify the peak; otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, and *Class 2 Mixture A Standard Solution*—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*

Standard Solution 1—[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with dimethylformamide to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of dimethylformamide, apply the stopper, cap, and mix.

Standard Solution 2—[NOTE—This solution is used for the quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylformamide RS and/or an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylacetamide RS to a suitable container; and dilute quantitatively, and stepwise if necessary, with 1,3-dimethyl-2-imidazolidinone to obtain a solution having a final concentration of 1/20 of the value stated in *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.

Test Stock Solution, Test Solution 1, and *Test Solution 2*—Proceed as directed for *Procedure A.*

Spiked Test Solution 1—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 1,* apply the stopper, cap, and mix.

Spiked Test Solution 2—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Solution 2* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 2,* apply the stopper, cap, and mix.

Chromatographic System—Proceed as directed for *Procedure C* under *Water-Soluble Articles.*

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution, Test Solution 1* and/or *Test Solution 2,* and *Spiked Test Solution 1* and/or *Spiked Test Solution 2* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$5(C/W)[r_U/(r_{ST} - r_U)]$$

in which C is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and r_{ST} are the peak responses of each residual solvent obtained from *Test Solution 1* or *Test Solution 2* and *Spiked Test Solution 1* or *Spiked Test Solution 2,* respectively.

Class 3 Residual Solvents

If only Class 3 solvents are present, the level of residual solvents is to be determined as directed under *Loss on Drying* ⟨731⟩. If the loss on drying value is greater than 0.5%, a water determination should be performed on the test sample as directed under *Water Determination* ⟨921⟩. Determine the water by *Method Ia*, unless otherwise specified in the individual monograph. If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option 1*), that residual solvent should be identified and quantified, and the procedures as described above, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for evaluation. USP Reference Standards, where available, should be used in these procedures. A flow diagram for the application of residual solvent limit tests is shown in *Figure 1*.

GLOSSARY

Genotoxic carcinogens: Carcinogens that produce cancer by affecting genes or chromosomes.

Lowest-observed-effect level (LOEL): The lowest dose of a substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in exposed humans or animals.

Modifying factor: A factor determined by professional judgment of a toxicologist and applied to bioassay data so that the data can be safely related to humans.

Neurotoxicity: The ability of a substance to cause adverse effects on the nervous system.

No-observed-effect level (NOEL): The highest dose of a substance at which there are no biologically significant increases in frequency or severity of any effects in exposed humans or animals.

Permitted daily exposure (PDE): The maximum acceptable intake per day of a residual solvent in pharmaceutical products.

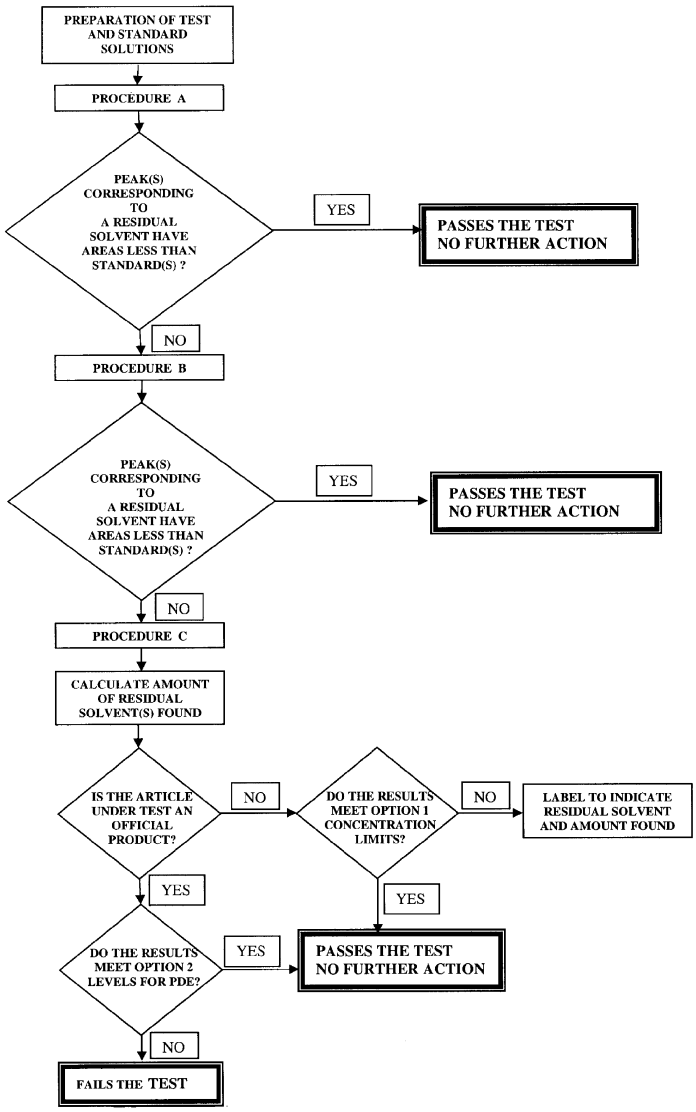


Figure 1. Diagram relating to the identification of residual solvents and the application of limit tests.

Reversible toxicity: The occurrence of harmful effects that are caused by a substance and that disappear after exposure to the substance ends.

Strongly suspected human carcinogen: A substance for which there is no epidemiological evidence of carcinogenesis but for which there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.

Teratogenicity: The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

APPENDIX 2. ADDITIONAL BACKGROUND

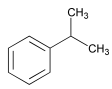
A2.1. Environmental Regulation of Organic Volatile Solvents

Several of the residual solvents frequently used in the production of pharmaceuticals are listed as toxic chemicals in Environmental Health Criteria (EHC) monographs and in the Integrated Risk Information System (IRIS). The objectives of such groups as the International Programme on Chemical Safety (IPCS), the United States Environmental Protection Agency (EPA), and the United States Food and Drug Administration (FDA) include the determination of acceptable exposure levels. The goal is maintenance of environmental integrity and protection of human health against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The procedures involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable, shorter term study data can be used with modification of the approach, such as use of larger safety factors. The approach described therein relates primarily to long-term or lifetime exposure of the general population in the ambient environment (i.e., ambient air, food, drinking water, and other media).

A2.2. Residual Solvents in Pharmaceuticals

Exposure limits in this General Chapter are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, the following specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits.

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER

Solvent	Other Names	Structure	Class
Acetic acid	Ethanoic acid	CH_3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH_3COCH_3	Class 3
Acetonitrile		CH_3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	*n*-Butyl alcohol Butan-1-ol	$CH_3(CH_2)_3OH$	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	$CH_3CH_2CH(OH)CH_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$CH_3COO(CH_2)_3CH_3$	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methylpropane	$(CH_3)_3COCH_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$CHCl_3$	Class 2
Cumene	Isopropylbenzene (1-Methylethyl)benzene		Class 3
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH_2ClCH_2Cl	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$H_2C=CCl_2$	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	$ClHC=CHCl$	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl cellosolve	$H_3COCH_2CH_2OCH_3$	Class 2
N,*N*-Dimethylacetamide	DMA	$CH_3CON(CH_3)_2$	Class 2
N,*N*-Dimethylformamide	DMF	$HCON(CH_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(CH_3)_2SO$	Class 3
1,4-Dioxane	*p*-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	CH_3CH_2OH	Class 3
2-Ethoxyethanol	Cellosolve	$CH_3CH_2OCH_2CH_2OH$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$CH_3COOCH_2CH_3$	Class 3
Ethylene glycol	1,2-Dihydroxyethane 1,2-Ethanediol	$HOCH_2CH_2OH$	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1′-Oxybisethane	$CH_3CH_2OCH_2CH_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$HCOOCH_2CH_3$	Class 3
Formamide	Methanamide	$HCONH_2$	Class 2
Formic acid		$HCOOH$	Class 3

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER *(Continued)*

Solvent	Other Names	Structure	Class
Heptane	*n*-Heptane	$CH_3(CH_2)_5CH_3$	Class 3
Hexane	*n*-Hexane	$CH_3(CH_2)_4CH_3$	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	$CH_3COOCH_2CH(CH_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	$CH_3COOCH(CH_3)_2$	Class 3
Methanol	Methyl alcohol	CH_3OH	Class 2
2-Methoxyethanol	Methyl cellosolve	$CH_3OCH_2CH_2OH$	Class 2
Methyl acetate	Acetic acid methyl ester	CH_3COOCH_3	Class 3
3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	$(CH_3)_2CHCH_2CH_2OH$	Class 3
Methylbutylketone	2-Hexanone Hexan-2-one	$CH_3(CH_2)_3COCH_3$	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylene chloride	Dichloromethane	CH_2Cl_2	Class 2
Methylethylketone	2-Butanone MEK Butan-2-one	$CH_3CH_2COCH_3$	Class 3
Methyl isobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$CH_3COCH_2CH(CH_3)_2$	Class 3
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	$(CH_3)_2CHCH_2OH$	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH_3NO_2	Class 2
Pentane	*n*-Pentane	$CH_3(CH_2)_3CH_3$	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	$CH_3(CH_2)_3CH_2OH$	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	$CH_3CH_2CH_2OH$	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	$(CH_3)_2CHOH$	Class 3
Propyl acetate	Acetic acid propyl ester	$CH_3COOCH_2CH_2CH_3$	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 2
Tetralin	1,2,3,4-Tetrahydronaphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH_3CCl_3	Class 1

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER *(Continued)*

Solvent	Other Names	Structure	Class
Trichloroethylene	1,1,2-Trichloroethene	$HClC=CCl_2$	Class 2
Xylene*	Dimethybenzene Xylol		Class 2

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

1. Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.
2. The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.
3. Residual solvents are unavoidable components in pharmaceutical production and will often be a part of medicinal products.
4. Residual solvents should not exceed recommended levels except in exceptional circumstances.
5. Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols such as those described, for example, by the Organization for Economic Cooperation and Development (OECD), EPA, and the FDA Red Book.

APPENDIX 3. PROCEDURES FOR ESTABLISHING EXPOSURE LIMITS

The Gaylor-Kodell method of risk assessment (Gaylor, D. W. and Kodell, R. L. Linear Interpolation Algorithm for Low Dose Assessment of Toxic Substance. *Journal of Environmental Pathology and Toxicology,* 4 : 305, 1980) is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for Class 1 residual solvents could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the no-observed-effect level (NOEL). Detection and quantification of these residual solvents should be performed by state-of-the-art analytical techniques.

Acceptable exposure levels in this General Chapter for Class 2 residual solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (page 5748 of *PF* 15(6) [Nov.–Dec. 1989]), and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (*Environmental Health Criteria 170,* WHO, 1994). These procedures are similar to those used by the U.S. EPA (IRIS) and the U.S. FDA *(Red Book)* and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values presented in *Table 2* of this document.

PDE is derived from the no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL), in the most relevant animal study as follows:

$$\text{PDE} = \frac{\text{NOEL} \times \text{Weight Adjustment}}{\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}} \quad (1)$$

The PDE is derived preferably from the NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of "uncertainty factors" used in Environmental Health Criteria (*Environmental Health Criteria 170,* WHO, Geneva, 1994) and "modifying factors" or "safety factors" in *Pharmacopeial Forum.* The assumption of 100 percent systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species
- F1 = 2 for extrapolation from dogs to humans
- F1 = 2.5 for extrapolation from rabbits to humans
- F1 = 3 for extrapolation from monkeys to humans
- F1 = 5 for extrapolation from rats to humans
- F1 = 10 for extrapolation from other animals to humans
- F1 = 12 for extrapolation from mice to humans

F1 takes into account the comparative surface area to body weight ratios for the species concerned and for man. Surface area (S) is calculated as:

$$S = kM^{0.67} \quad (2)$$

in which M = body weight, and the constant k has been taken to be 10. The body weights used in the equation are those shown below in *Table A3.-1*.

F2 = A factor of 10 to account for variability between individuals. A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this General Chapter.

F3 = A variable factor to account for toxicity studies of short-term exposure.
- F3 = 1 for studies that last at least one half-lifetime (1 year for rodents or rabbits; 7 years for cats, dogs, and monkeys).
- F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.
- F3 = 2 for a 6-month study in rodents, or a 3.5-year study in nonrodents.
- F3 = 5 for a 3-month study in rodents, or a 2-year study in nonrodents.
- F3 = 10 for studies of a shorter duration.

In all cases, the higher factor has been used for study durations between the time points (e.g., a factor of 2 for a 9-month rodent study).

F4 = A factor that may be applied in cases of severe toxicity, e.g., nongenotoxic carcinogenicity, neurotoxicity, or teratogenicity. In studies of reproductive toxicity, the following factors are used:
- F4 = 1 for fetal toxicity associated with maternal toxicity
- F4 = 5 for fetal toxicity without maternal toxicity
- F4 = 5 for a teratogenic effect with maternal toxicity
- F4 = 10 for a teratogenic effect without maternal toxicity

F5 = A variable factor that may be applied if the no-effect level was not established.

When only a LOEL is available, a factor of up to 10 can be used depending on the severity of the toxicity. The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kilograms (kg). This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult

patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarized in *Pharmeuropa,* Vol. 9, No. 1, Supplement, April 1997, page S24. The NOEL is calculated to be 50.7 mg kg^{-1} day^{-1}. The PDE for acetonitrile in this study is calculated as follows:

$$\text{PDE} = \frac{50.7\ \text{mg kg}^{-1}\ \text{day}^{-1} \times\ 50\ \text{kg}}{12\times10\times5\times1\times1} = 4.22\ \text{mg day}^{-1}$$

In this example,

F1 = 12 to account for the extrapolation from mice to humans
F2 = 10 to account for differences between individual humans
F3 = 5 because the duration of the study was only 13 weeks
F4 = 1 because no severe toxicity was encountered
F5 = 1 because the no-effect level was determined

A3.-1. - Values Used in the Calculations in This Document

Rat body weight	425 g
Pregnant rat body weight	330 g
Mouse body weight	28 g
Pregnant mouse body weight	30 g
Guinea-pig body weight	500 g
Rhesus monkey body weight	2.5 kg
Rabbit body weight (pregnant or not)	4 kg
Beagle dog body weight	11.5 kg
Rat respiratory volume	290 L/day
Mouse respiratory volume	43 L/day
Rabbit respiratory volume	1440 L/day
Guinea-pig respiratory volume	430 L day
Human respiratory volume	28,800 L/day
Dog respiratory volume	9000 L/day
Monkey respiratory volume	1150 L/day
Mouse water consumption	5 mL/day
Rat water consumption	30 mL/day
Rat food consumption	30 g/day

The equation for an ideal gas, $PV = nRT$, is used to convert concentrations of gases used in inhalation studies from units of ppm to units of mg/L or mg/m^3. Consider as an example the rat reproductive toxicity study by inhalation of carbon tetrachloride (molecular weight 153.84) summarized in *Pharmeuropa,* Vol. 9, No. 1, Supplement, April 1997, page S9.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300\times10^{-6}\ \text{atm}\times153\ 840\ \text{mg mol}^{-1}}{0.082\ \text{L at mK}^{-1}\ \text{mol}^{-1}\times298\ \text{K}} = \frac{46.15\ \text{mg}}{24.45\ \text{L}} = 1.89\ \text{mg/L}$$

The relationship 1000 L = 1 m^3 is used to convert to mg/ m^3.