Q3c杂质: 残留溶剂的指导原则(全文)

中国化学化工论坛

从1994年起，ICH（人用药物注册技术要求国际协调会议）开始着手制定《Q3c杂质：残留溶剂的指导原则》。该原则中将常用的溶剂分为第一类、第二类和第三类，对各类溶剂的限度有不同要求。此原则于1997年12月24日正式生效，在欧盟、日本、美国实施。

中国药典2000年版制定了“有机溶剂残留量测定法”，要求对生产过程中引入的有害有机溶剂残留量进行检查。这些有机溶剂包括苯、氯仿、二氧六环、二氯甲烷、吡啶、甲苯和环氧乙烷。生产过程中如涉及其它需要检查的有害有机溶剂，则应在各品种项下另作规定。此版中国药典未对有机溶剂进行分类，未对上述几种溶剂外的其他有机溶剂及其限度进行规定。不过，为了与国外医药行业的接轨，我国食品药品监督管理局将逐渐制定相关指导原则。

Q3C为该指导原则的编号,即Q3代表不纯物测试.

Q3C: Impurities: Guideline for Residual Solvents

Therapeutic Products Programme

Holland Cross, Tower B

1600 Scott Street

A.L.# 3102D1

OTTAWA (Ontario)

K1A 1B6

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To: Associations, Registrars of Pharmacy, Registrars of Medicine

I am pleased to inform you of the release of the *International Conference on Harmonisation of Technical Requirements for the Registration of Pharma-ceuticals for Human Use* (ICH) / Therapeutic Products Programme (TPP) guideline, "Impurities: Guideline for Residual Solvents". This guideline has been developed by an ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and the United States.

The Therapeutic Products Programme has adopted this international guideline. In accordance with ICH rules, the document was adopted verbatim. This guideline represents an approach that will be considered accepta-ble for the review of new and "existing" drugs. In the context of this guideline, an "existing" drug is one for which a Notice of Compliance has previously been issued pursuant to Division 8 of the *Food and Drug Regulations* (e.g., generic products).

Innovator and generic products are covered by this guideline as the control of residual solvents is considered equally pertinent to establishing the accepta-bility of the specifica-tions for drugs from both types of sources. The expansion on ICH concepts to generic drugs is not new, as reflected in the current TPP guideline "Impurities in New Drug Substances" (1995).

The guideline is available through Internet at **www.hc-sc.gc.ca/hpb-dgps/therapeut**. For those clients who do not have access to Internet, printed copies will be available through Health Canada Publications, telephone (613) 954-5995 or fax (613) 941-5366.

Should you have any questions regarding the content of the guideline, please contact:

Sultan Ghani

A/Manager Division of Pharmaceutical Quality

Bureau of Pharmaceutical Assessment

Therapeutic Products Programme

Health Canada

A.L. 0202A2

Finance Building

Tunney's Pasture

OTTAWA, Ontario

K1A 1B6

Telephone: (613) 941-3184

Facsimile: (613) 941-0571

E-mail: sultan_ghani@hc-sc.gc.ca

Original signed by

Dann M. Michols

Director General

THERAPEUTIC PRODUCTS PROGRAMME GUIDELINE

ICH HARMONISED TRIPARTITE GUIDELINE

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS

Published by authority of the

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For more information, please contact:

Therapeutic Products Programme

Health Canada

Tunney's Pasture

Ottawa, Ontario

K1A 0L2

Disclaimer

The material herein was prepared under the direction of the Therapeutic Products Programme, Health Canada. No changes are permitted.

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Therapeutic Products Programme Webmaster: Pete Nilson

Telephone: (613) 941-1601

Facsimile: (613) 941-0825

Available in Canada through Health Canada Publications

Brooke Claxton Building

A.L. #0913A

Tunney's Pasture

Ottawa, Ontario

K1A 0K9

Tel: (613) 954-5995

Fax: (613) 941-5366

Internet: www.hc-sc.gc.ca/hpb-dgps/therapeut

tp_webmaster@hc-sc.gc.ca

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FOREWORD

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The Therapeutic Products Programme (TPP) has adopted this guideline and reproduced it in this document. This guideline represents an approach that will be considered acceptable for the review of new and "existing" drugs. In the context of this guideline, an "existing" drug is one for which a Notice of Compliance has previously been issued pursuant to Division 8 of the Food and Drug Regulations (e.g., generic products).

Innovator and generic products are covered by this guideline as the control of residual solvents is considered equally pertinent to establishing the acceptability of the specifications for drugs from both types of sources. The expansion on ICH concepts to generic drugs is not new, as reflected in the current TPP guideline *Impurities in New Drug Substances* (1995).

Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. Submission sponsors may discuss, in advance, alternate approaches with the Directorate to avoid the withdrawal/ rejection of a submission.

TABLE OF CONTENTS

1. INTRODUCTION

The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Residual solvents in pharmaceuticals are defined here 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 solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guideline 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.

Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet 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. Some 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. Some 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 guideline is given in Appendix 1.

The lists are not exhaustive and other solvents can be used and later added to the lists. Recommended limits of Class 1 and 2 solvents or classification of solvents may change as new safety data becomes available. Supporting safety data in a marketing application for a new drug product containing a new solvent may be based on concepts in this guideline or the concept of qualification of impurities as expressed in the guideline for drug substance (Q3A, Impurities in New Drug Substances) or drug product (Q3B, Impurities in New Drug Products), or all three guidelines.

2. SCOPE OF THE GUIDELINE

Residual solvents in drug substances, excipients, and drug products are within the scope of this guideline. Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only considered necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug products. Although manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level equal to or below that recommended in this guideline, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. Drug product should also be tested if a solvent is used during its manufacture.

This guideline does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

The guideline applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases such as short-term (30 days or less) or topical application. Justification for these levels should be made on a case-by-case basis. See Appendix 2 of this document for additional background information related to residual solvents.

3. GENERAL PRINCIPLES

3.1 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 new term "permitted daily exposure" (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADI's of the same substance.

Residual solvents assessed in this guideline 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 solvents: Solvents to be avoided-

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Class 2 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 solvents: Solvents with low toxic potential-

Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDE's of 50 milligrams (mg) or more per day.

3.2 Methods for Establishing Exposure Limits

The method used to establish permitted daily exposures for residual solvents is presented in Appendix 3. Summaries of the toxicity data that were used to establish limits are published in Pharmeuropa, Vol. 9, No. 1, Supplement, April 1997.

3.3 Options for Describing Limits of Class 2 Solvents

Two options are available when setting limits for Class 2 solvents.

Option 1: The concentration limits in parts per million (ppm) stated in Table 2 can be used. They were calculated using equation (1) below by assuming a product mass of 10 grams (g) administered daily.

(1) Concentration (ppm) = (1000 * PDE) / dose

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

These limits are considered acceptable for all substances, excipients, or products. Therefore, this option may be applied if the daily dose is not known or fixed. If all excipients and drug substances in a formulation meet the limits given in Option 1, then 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 should be considered under Option 2.

Option 2: It is not considered necessary for each component of the drug product to comply with the limits given in Option 1. The PDE in terms of mg/day as stated in Table 2 can be used with the known maximum daily dose and equation (1), as shown in Option 1 in the previous paragraph, to determine the concentration of residual solvent allowed in 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 and the limits should 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 use of Option 1 and Option 2 applied to acetonitrile 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 mass 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	Acetonitrile content	Daily exposure
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	400 ppm	0.36 mg
Excipient 2	3.8 g	800 ppm	3.04 mg

Drug product	5.0 g	728 ppm	3.64 mg

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 product meets the Option 2 limit of 4.1 mg per day and thus conforms to the recommendations in this guideline.

Consider another example using acetonitrile as residual solvent. The maximum administered daily mass 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	Acetonitrile content	Daily exposure
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	2000 ppm	1.80 mg
Excipient 2	3.8 g	800 ppm	3.04 mg
Drug product	5.0 g	1016 ppm	5.08 mg

In this example, the product meets neither the Option 1 nor the Option 2 limit according to this summation. 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 during formulation to the allowed limit, then the manufacturer of the drug product should take other steps to reduce the amount of acetonitrile in the drug product. If all of these steps fail to reduce the level of residual solvent, in exceptional cases the manufacturer could provide a summary of efforts made to reduce the solvent level to meet the guideline value, and provide a risk-benefit analysis to support allowing the product to be utilized with residual solvent at a higher level.

3.4 Analytical Procedures

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Any harmonized procedures for determining levels of residual solvents as described in the pharmacopoeias should be used, if feasible. Otherwise, manufacturers would be free to select the most appropriate validated analytical procedure for a particular application. If only Class 3 solvents are present, a nonspecific method such as loss on drying may be used.

Validation of methods for residual solvents should conform to ICH guidelines "Q2A Text on Validation of Analytical Procedures" and "Q2B Validation of Analytical Procedures: Methodology."

3.5 Reporting Levels of Residual Solvents

Manufacturers of pharmaceutical products need certain information about the content of residual solvents in excipients or drug substances in order to meet the criteria of this guideline. The following statements are given as acceptable examples of the information that could be provided from a supplier of excipients or drug substances to a pharmaceutical manufacturer. The supplier might choose one of the following as appropriate:

- Only Class 3 solvents are likely to be present. Loss on drying is less than 0.5 percent.
- Only Class 2 solvents X, Y, ... are likely to be present. All are below the Option 1 limit. (Here the supplier would name the Class 2 solvents represented by X, Y, ...)
- Only Class 2 solvents X, Y, ... and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5 percent.

If Class 1 solvents are likely to be present, they should be identified and quantified. "Likely to be present" refers to the solvent used in the final manufacturing step and to solvents that are used in earlier manufacturing steps and not removed consistently by a validated process.

If solvents of Class 2 or Class 3 are present at greater than their Option 1 limits or 0.5 percent, respectively, they should be identified and quantified.

4. LIMITS OF RESIDUAL SOLVENTS

4.1 Solvents to Be Avoided

Solvents in Class 1 should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. 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 a review of the safety data.

Table 1. - Class 1 Solvents in Pharmaceutical Products (solvents that should be avoided)

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

4.2 Solvents to Be Limited

Solvents in Table 2 should be limited in pharmaceutical products because of their inherent toxicity. PDE's are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

Table 2. - Class 2 Solvents in Pharmaceutical Products

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-Dichloroethane	18.7	1870
Dichloromethane	6.0	600
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
Ethyleneglycol	6.2	620

Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1180
N-Methylpyrrolidone	48.4	4840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene*	21.7	2170

4.3 Solvents with Low Toxic Potential

Solvents in Class 3 (shown in Table 3) may be regarded as less toxic and of lower risk to human health. 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 solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5,000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice (GMP).

Table 3. - Class 3 Solvents Which Should Be Limited by GMP or Other Quality-Based Requirements

- Acetic acid
- Acetone
- Anisole
- 1-Butanol
- 2-Butanol
- Butyl acetate
- tert-Butylmethyl ether
- Cumene
- Dimethyl sulfoxide
- Ethanol
- Ethyl acetate
- Ethyl ether
- Ethyl formate
- Formic acid
- Heptane

- Isobutyl acetate
- Isopropyl acetate
- Methyl acetate
- 3-Methyl-1-butanol
- Methylethyl ketone
- Methylisobutyl ketone
- 2-Methyl-1-propanol
- Pentane
- 1-Pentanol
- 1-Propanol
- 2-Propanol
- Propyl acetate
- Tetrahydrofuran

4.4 Solvents for Which No Adequate Toxicological Data Were Found

The following solvents (Table 4) may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDE were found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

Table 4. - Solvents for Which No Adequate Toxicological Data Were Found

- 1,1-Diethoxypropane
- 1,1-Dimethoxymethane
- 2,2-Dimethoxypropane
- Isooctane
- Isopropyl ether
- Methylisopropyl ketone
- Methyltetrahydrofuran
- Petroleum ether
- Trichloroacetic acid
- Trifluoroacetic acid

GLOSSARY

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

LOEL: Abbreviation for lowest-observed effect level.

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

Modifying factor: A factor determined by professional judgment of a toxicologist and applied to bioassay data to relate that data safely to humans.

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

NOEL: Abbreviation for no-observed-effect level.

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

PDE: Abbreviation for permitted daily exposure.

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

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

Strongly suspected human carcinogen: A substance for which there is no epidemiological evidence of carcinogenesis but 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 1
LIST OF SOLVENTS INCLUDED IN THE GUIDELINE

Solvent	*Other Names*	*Structure*	*Class*
Acetic acid	Ethanoic acid	CH3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH3COCH3	Class 3
Acetonitrile		CH3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	Butan-1-ol *n*-butyl alcohol	CH3(CH2)3OH	Class 3
2-Butanol	Butan-2-ol *sec*-butyl alcohol	CH3CH2CH(OH)CH3	Class 3
Butyl acetate	Acetic acid butyl ester	CH3COO(CH2)3CH3	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methylpropane	(CH3)3COCH3	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	CHCl3	Class 2
Cumene	Isopropylbenzene (1-Methyl)ethylbenzene		Class 3
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*Sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH2ClCH2Cl	Class 1

Solvent	*Other Names*	*Structure*	*Class*
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	H2C=CCl2	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	ClHC=CHCl	Class 2
Dichloromethane	Methylene chloride	CH2Cl2	Class 2
1,2-Dimethoxyethane	Ethylene glycol dimethyl ether Monoglyme Dimethyl Cellosolve	H3COCH2CH2OCH3	Class 2
N,N-Dimethylacetamide	DMA	CH3CON(CH3)2	Class 2
N,N-Dimethylformamide	DMF	HCON(CH3)2	Class 2
Dimethylsulfoxyde	Methylsulfinylmethane Methyl sulfoxide DMSO	(CH3)2SO	Class 3
1,4-Dioxane	p-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	CH3CH2OH	Class 3
2-Ethoxyethanol	Cellosolve	CH3CH2OCH2CH2OH	Class 2
Ethyl acetate	Acetic acid ethyl ester	CH3COOCH2CH3	Class 3
Ethylene glycol	1,2-Dihydroxyethane Ethane-1,2-diol	HOCH2CH2OH	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1'-Oxybisethane	CH3CH2OCH2CH3	Class 3
Ethyl formate	Formic acid ethyl ester	HCOOCH2CH3	Class 3
Formamide	Methanamide	HCONH2	Class 2
Formic acid		HCOOH	Class 3
Heptane	*n*-Heptane	CH3(CH2)5CH3	Class 3

Solvent	*Other Names*	*Structure*	*Class*
Hexane	*n*-Hexane	CH3(CH2)4CH3	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	CH3COOCH2CH(CH3)2	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	CH3COOCH(CH3)2	Class 3
Methanol	Methyl alcohol	CH3OH	Class 2
2-Methoxyethanol	Methyl Cellosolve	CH3OCH2CH2OH	Class 2
Methyl acetate	Acetic acid methyl ester	CH3COOCH3	Class 3
3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	(CH3)2CHCH2CH2OH	Class 3
Methylbutyl ketone	Hexan-2-one 2-Hexanone	CH3(CH2)3COCH3	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylethylcetone	MEK Butan-2-one 2-Butanone	CH3CH2COCH3	Class 3
Methylisobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	CH3COCH2CH(CH3)2	Class 3
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	(CH3)2CHCH2OH	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH3NO2	Class 2
Pentane	*n*-Pentane	CH3(CH2)3CH3	Class 3

Solvent	*Other Names*	*Structure*	*Class*
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	CH3(CH2)3CH2OH	Class 3
1-Propanol	Propyl alcohol Propan-1-ol	CH3CH2CH2OH	Class 3
2-Propanol	Isopropyl alcohol Propan-2-ol	(CH3)2CHOH	Class 3
Propyl acetate	Acetic acid propyl ester	CH3COOCH2CH2CH3	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 3
Tetralin	1,2,3,4-Tetrahydronaphtalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH3CCl3	Class 1
1,1,2-Trichloroethene	Trichloroethene	HClC=CCl2	Class 2
Xylene*	Dimethylbenzene Xylol		Class 2

* usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethylbenzene

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 the Integrated Risk Information System (IRIS). The objectives of such groups as the IPCS, the U.S. Environmental Protection Agency (EPA), and FDA include the determination of acceptable exposure levels. The goal is protection of human health and maintenance of environmental integrity against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The methods 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 guideline are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, some 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. They are as follows:

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 drug 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 Cooperation and Development, EPA, and the FDA Red Book.

APPENDIX 3

METHODS FOR ESTABLISHING EXPOSURE LIMITS

The Gaylor-Kodell method of risk assessment (Gaylor, D. W., and R. L. Kodell, "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 solvents could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the NOEL. Detection and quantitation of these solvents should be by state-of-the-art analytical techniques. Acceptable exposure levels in this guideline for Class 2 solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (Pharmacopeial Forum, Nov-Dec 1989), and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (EHC 170, WHO, 1994). These methods 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 tabulated in Section 4 of this document.

PDE is derived from the NOEL or the LOEL in the most relevant animal study as follows:

(1)

PDE = (NOEL * Weight Adjustment) / (F1 * F2 * F3 * F4 * F5)

The PDE is derived preferably from a 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 EHC (EHC 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 = 5 for extrapolation from rats to humans

F1 = 12 for extrapolation from mice to humans

F1 = 2 for extrapolation from dogs to humans

F1 = 2.5 for extrapolation from rabbits to humans

F1 = 10 for extrapolation from other animals to humans.

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

(2)

$S = kM^{0.67}$

in which M = body mass, 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 guideline.

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 an LOEL is available, a factor of up to 10 could 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:

PDE = (50.7 mg kg^{-1} day^{-1} * 50 kg) / (12 * 10 * 5 * 1 * 1)

PDE = 4.22 mg day^{-1}

In this example,

F1 = 12 to account for the extrapolation from mice to humans

F2 = 10 to account for the 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.

Table 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/cubic meter (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.

n / V = P / RT

P / RT = (300 * 10^{-6} atm * 153 840 mg mol^{-1}) / (0.082 L atm K^{-1} mol^{-1} * 298 K) = 46.15 mg / 24.45 L = 1.89 mg/L

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