INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS
Q3C(R8)

Current *Step 4* version
dated 22 April 2021

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

Q3C(R8)
Document History

Code	History	Date
Parent Guideline: Impurities: Guideline for Residual Solvents		
Q3C	Approval by the Steering Committee under *Step 2* and release for public consultation.	6 November 1996
Q3C	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	17 July 1997
Revision of the PDE information for THF contained in the Parent Guideline		
Q3C(R1) Note: Prior to adding the revision to the parent Guideline in November 2005, the code was Q3C(M) for THF.	Permissible Daily Exposure (PDE) for Tetrahydrofuran (THF): revision of PDE based on new toxicological data. Approval by the Steering Committee of the new PDE for THF under *Step 2* and release for public consultation.	20 July 2000
Q3C(R1) Note: Prior to adding the revision to the parent Guideline in November 2005, the code was Q3C(M) for THF.	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	12 September 2002
Revision of PDE information for NMP contained in the Parent Guideline		
Q3C(R2) Note: Prior to adding the revision to the parent Guideline in November 2005, the code was Q3C(M) for NMP.	Permissible Daily Exposure (PDE) for N-Methylpyrrolidone (NMP): revision of PDE based on new toxicological data. Approval by the Steering Committee of the Revision under *Step 2* and release for public consultation.	20 July 2000
Q3C(R2) Note: Prior to adding the revision to the parent Guideline in November 2005, the code was Q3C(M) for NMP.	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	12 September 2002
Q3C(R3) Note: Prior to adding the corrigendum to the parent Guideline in November 2005, the code was Q3C(M) for NMP.	Corrigendum to calculation formula approved by the Steering Committee.	28 October 2002
Q3C(R3)	The parent Guideline is now renamed Q3C(R3) as the two updates (PDE for N-Methylpyrrolidone and PDE for Tetrahydrofuran) and the corrigendum of the update for NMP have been added to the parent Guideline.	November 2005

Parent Guideline: Impurities: Guideline for Residual Solvents

Q3C(R4)	Update of Table 2, Table 3 and Appendix 1 to reflect the revision of the PDEs for N-Methylpyrrolidone and Tetrahydrofuran.	February 2009

Revision of PDE information for Cumene contained in the Parent Guideline

Q3C(R5)	Permissible Daily Exposure (PDE) for Cumene: revision of PDE based on new toxicological data. Approval by the Steering Committee under *Step 2* and release for public consultation.	26 March 2010
Q3C(R5)	Approval of the PDE for Cumene by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies. The PDE for Cumene document has been integrated as part IV in the core Q3C(R4) Guideline which was then renamed Q3C(R5). The Table 2, Table 3 and Appendix 1 have been updated to reflect the revision of the PDE for Cumene.	4 February 2011

Revision of PDE information for Methylisobutylketone contained in the Parent Guideline and to include a PDE for Triethylamine

Q3C(R6)	Permissible Daily Exposure (PDE) for Triethylamine and Methylisobutylketone: revision of PDE based on new toxicological data. Approval by the Assembly under Step 2 and release for public consultation.	9 November 2016
Q3C(R6)	Approval of the PDE for Triethylamine and Methylisobutylketone by the Assembly under *Step 4* and recommendation for adoption to the three ICH regulatory bodies. The PDE for Triethylamine and Methylisobutylketone document has been integrated as part V in the core Q3C(R5) Guideline which was then renamed Q3C(R6). The Table 2, Table 3 and Appendix 1 have been updated to reflect the revision of the PDE for Triethylamine and Methylisobutylketone.	9 November 2016

Correction of the PDE for Ethyleneglycol

Q3C(R7)	Correction for the PDE and concentration limit for Ethyleneglycol on Table 2 page 6, as per the correct value calculated in Pharmeuropa, Vol. 9, No. 1, Supplement, April 1997 S36.	15 October 2018
Q3C(R6)	Further to archival searches related to the Permissible Daily Exposure (PDE) for ethyleneglycol, the Q3C(R7) Guideline was reverted back to the Q3C(R6) Guideline. Further information is provided in the cover statement dated 22 July 2019.	4 October 2019

Addition of PDE for 2-Methyltetrahydrofuran (2-MTHF), Cyclopentyl Methyl Ether (CPME), and Tertiary Butyl Alcohol (TBA)

Q3C(R8)	Endorsement of Part VI of Q3C(R8) (PDEs for 2-MTHF, CPME, TBA) by the Members of the ICH Assembly under *Step 2* and released for public consultation.	25 March 2020
Q3C(R8)	Adoption of Part VI of Q3C(R8) (PDEs for 2-MTHF, CPME, TBA) by the Regulatory Members of the ICH Assembly under *Step 4* .	22 April 2021
Q3C(R8)	Editorial corrections approved by the Q3C(R8) Topic Leaders within the core text (page 8 & deletion of "Methyltetrahydrofuran" from Table 4 on page 9).	16 August 2022

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS

ICH Harmonised Guideline

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PART I:
IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 17 July 1997, this Guideline is recommended for adoption to the three regulatory parties to ICH

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 in 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 necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug product. 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* 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 "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

Non-genotoxic 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 PDEs of 50 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 ppm stated in Table 2 can be used. They were calculated using equation (1) below by assuming a product mass of 10 g administered daily.

$$\text{Concentration (ppm)} = \frac{1000 \text{ x PDE}}{\text{dose}} \qquad (1)$$

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) above 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, 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 utilised with residual solvent at a higher level.

3.4 Analytical Procedures

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Any harmonised 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 non-specific method such as loss on drying may be used.

Validation of methods for residual solvents should conform to ICH guidelines *Text on Validation of Analytical Procedures* and *Extension of the ICH Text on Validation of Analytical Procedures*.

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%.
- 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%.

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%, 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. 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-Dichloroethene	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. PDEs 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
Cumene[1]	0.7	70
Cyclohexane	38.8	3880
Cyclopentyl methyl ether[2]	15.0	1500
1,2-Dichloroethene	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
Methylisobutylketone[3]	45	4500
N-Methylpyrrolidone[4]	5.3	530

[1] The information included for Cumene reflects that included in the *Revision of PDE Information for Cumene* which reached *Step 4* in February 2011 and was subsequently incorporated into the core Guideline. See Part IV (pages 24-27).

[2] The information included for Cyclopentyl Methyl Ether reflects that included in the Revision of PDE Information for 2-MTHF, CPME, and TBA which reached *Step 4* in April 2021 and was subsequently incorporated into the core Guideline. See Part VI (pages 35-45).

[3] The information included for Methylisobutylketone reflects that included in the *Revision of PDE Information for Methylisobutylketone* which reached *Step 4* in November 2016 and was subsequently incorporated into the core Guideline. See Part V (pages 28-34).

Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tertiary-butyl alcohol[5]	35	3500
Tetrahydrofuran[6]	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene*	21.7	2170

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

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 5000 ppm or 0.5% 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.

TABLE 3. Class 3 solvents which should be limited by GMP or other quality-based requirements.

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	2-Methyl-1-propanol
Dimethyl sulfoxide	2-Methyltetrahydrofuran[7]

[4] The information included for N-Methylpyrrolidone reflects that included in the *Revision of PDE Information for NMP* which reached *Step 4* in September 2002 (two mistyping corrections made in October 2002), and was incorporated into the core guideline in November 2005. See Part III (pages 22-23).

[5] The information included for Tertiary-butyl Alcohol reflects that included in the Revision of PDE Information for 2-MTHF, CPME, and TBA which reached *Step 4* in April 2021 and was subsequently incorporated into the core Guideline. See Part VI (pages 35-45).

[6] The information included for Tetrahydrofuran reflects that included in the *Revision of PDE Information for THF* which reached *Step 4* in September 2002, and was incorporated into the core guideline in November 2005. See Part II (pages 20-21).

Ethanol	Pentane
Ethyl acetate	1-Pentanol
Ethyl ether	1-Propanol
Ethyl formate	2-Propanol
Formic acid	Propyl acetate
	Triethylamine[8]

[7] The information included for 2-Methyltetrahydrofuran reflects that included in the Revision of PDE Information for 2-MTHF, CPME, and TBA which reached *Step 4* in April 2021 and was subsequently incorporated into the core Guideline. See Part VI (pages 35-45).

[8] The information included for Triethylamine reflects that included in the *Revision of PDE Information for Triethylamine* which reached *Step 4* in November 2016 and was subsequently incorporated into the core Guideline. See Part V (pages 28-34).

4.4 Solvents for which No Adequate Toxicological Data was 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 was found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

TABLE 4. Solvents for which no adequate toxicological data was found.

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

GLOSSARY

Genotoxic Carcinogens:
Carcinogens which 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.

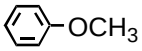
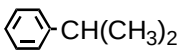
Permitted Daily Exposure:
The maximum acceptable intake per day of residual solvent in pharmaceutical products.

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.

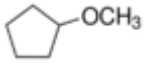
Teratogenicity:
The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

APPENDIX 1. LIST OF SOLVENTS INCLUDED IN THE GUIDELINE

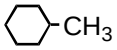
Solvent	***Other Names***	***Structure***	***Class***
Acetic acid	Ethanoic acid	CH3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH3COCH3	Class 3
Acetonitrile		CH3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	*n*-Butyl alcohol Butan-1-ol	CH3(CH2)3OH	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	CH3CH2CH(OH)CH3	Class 3
Butyl acetate	Acetic acid butyl ester	CH3COO(CH2)3CH3	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methyl-propane	(CH3)3COCH3	Class 3
Tertiary-butyl alcohol[1]	*t*-Butyl alcohol *tert*-butanol	(CH3)3COH	Class 2
Carbon tetrachloride	Tetrachloromethane	CCl4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	CHCl3	Class 2
Cumene[2]	Isopropylbenzene (1-Methyl)ethylbenzene		Class 2
Cyclohexane	Hexamethylene		Class 2

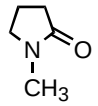
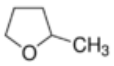
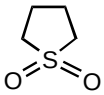
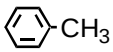
[1] The information included for Tertiary-butyl alcohol reflects that included in the Revision of PDE Information for 2-MTHF, CPME, and TBA which reached *Step 4* in April 2021 and was subsequently incorporated into the core Guideline. See Part VI (pages 35-45).

[2] The information included for Cumene reflects that included in the *Revision of PDE Information for Cumene* which reached *Step 4* in February 2011 and was subsequently incorporated into the core Guideline. See Part IV (pages 24-27).

Solvent	*Other Names*	*Structure*	*Class*
Cyclopentyl methyl ether[3]	CPME		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH2ClCH2Cl	Class 1
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	Ethyleneglycol 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
Dimethyl sulfoxide	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
Ethyleneglycol	1,2-Dihydroxyethane 1,2-Ethanediol	HOCH2CH2OH	Class 2

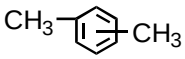
[3] The information included for Cyclopentyl methyl ether reflects that included in the Revision of PDE Information for 2-MTHF, CPME, and TBA which reached *Step 4* in April 2021 and was subsequently incorporated into the core Guideline. See Part VI (pages 35-45).

Solvent	***Other Names***	***Structure***	***Class***
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
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	2-Hexanone Hexan-2-one	CH3(CH2)3COCH3	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylethyl ketone	2-Butanone MEK Butan-2-one	CH3CH2COCH3	Class 3
Methylisobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	CH3COCH2CH(CH3)2	Class 2
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	(CH3)2CHCH2OH	Class 3

Solvent	*Other Names*	*Structure*	*Class*
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
2-Methyltetrahydrofuran[4]	2-methyloxolane tetrahydrosylvan		Class 3
Nitromethane		CH3NO2	Class 2
Pentane	*n*-Pentane	CH3(CH2)3CH3	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	CH3(CH2)3CH2OH	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	CH3CH2CH2OH	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	(CH3)2CHOH	Class 3
Propyl acetate	Acetic acid propyl ester	CH3COOCH2CH2CH3	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran[5]	Tetramethylene oxide Oxacyclopentane		Class 2
Tetralin	1,2,3,4-Tetrahydro-naphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH3CCl3	Class 1
1,1,2-Trichloroethene	Trichloroethene	HClC=CCl2	Class 2

[4] The information included for 2-methyltetrahydrofuran reflects that included in the Revision of PDE Information for 2-MTHF, CPME, and TBA which reached *Step 4* in April 2021 and was subsequently incorporated into the core Guideline. See Part VI (pages 35-45).

[5] The information included for Tetrahydrofuran reflects that included in the *Revision of PDE Information for THF* which reached *Step 4* in September 2002, and was incorporated into the core guideline in November 2005. See Part II (pages 20-21).

Solvent	***Other Names***	***Structure***	***Class***
Triethylamine	N,N-Diethylethanamine	$N(CH_2CH_3)_3$	Class 3
Xylene*	Dimethybenzene Xylol		Class 2

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

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 International Programme on Chemical Safety (IPCS), the United States Environmental Protection Agency (USEPA), and the United States Food and Drug Administration (USFDA) 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 *life-time 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:

1) Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.

2) The assumption of life-time 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 OECD, EPA, and the FDA Red Book.

APPENDIX 3. METHODS 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. J Environ. Pathology, *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 no-observed-effect level (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 (Environmental Health Criteria 170, WHO, 1994). These methods are similar to those used by the USEPA (IRIS) and the USFDA (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 no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL) in the most relevant animal study as follows:

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

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 Environmental Health Criteria (Environmental Health Criteria 170, World Health Organization, Geneva, 1994), and "modifying factors" or "safety factors" in Pharmacopeial Forum. The assumption of 100% 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 = 3 for extrapolation from monkeys 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:

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

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 non-rodents.

F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents.

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., non-genotoxic 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 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:

$$\text{PDE} = \frac{50.7 \text{ mg kg}^{-1} \text{ day}^{-1} \text{ x } 50 \text{ kg}}{12 \text{ x } 10 \text{ x } 5 \text{ x } 1 \text{ x } 1} = 4.22 \text{ mg day}^{-1}$$

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

Table A3.1. Values used in the calculations in this document.

rat body weight	425 g	mouse respiratory volume	43 L/day

pregnant rat body weight	330 g	rabbit respiratory volume	1440 L/day
mouse body weight	28 g	guinea pig respiratory volume	430 L/day
pregnant mouse body weight	30 g	human respiratory volume	28,800 L/day
guinea pig body weight	500 g	dog respiratory volume	9,000 L/day
Rhesus monkey body weight	2.5 kg	monkey respiratory volume	1,150 L/day
rabbit body weight (pregnant or not)	4 kg	mouse water consumption	5 mL/day
beagle dog body weight	11.5 kg	rat water consumption	30 mL/day
rat respiratory volume	290 L/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) is summarized in Pharmeuropa, Vol. 9, No. 1, Supplement, April 1997, page S9.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300 \times 10^{-6} \text{ atm} \times 153840 \text{ mg mol}^{-1}}{0.082 \text{ L atm K}^{-1} \text{ mol}^{-1} \times 298 \text{ K}} = \frac{46.15 \text{ mg}}{24.45 \text{ L}} = 1.89 \text{ mg / L}$$

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

PART II:
IMPURITIES: RESIDUAL SOLVENTS (MAINTENANCE)
PDE FOR TETRAHYDROFURAN
ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 12 September, 2002 and incorporated into the core Guideline in November 2005, this Guideline is recommended for adoption to the three regulatory parties to ICH

The ICH Q3C guidance reached *Step 5* in December of 1997. It had been agreed by the members of the Expert Working Group (EWG) that the permissible daily exposure (PDE) could be modified if reliable and more relevant toxicity data was brought to the attention of the group. In 1999, a maintenance agreement was instituted and a Maintenance EWG was formed. The agreement provided for the re-visitation of solvent PDEs and allowed for minor changes to the guidance that included the existing PDEs. It was also agreed that new solvents and PDEs could be added based upon adequate toxicity data.

The EWG visited new toxicity data for the solvent tetrahydrofuran (THF) late last year and earlier this year. The data in review was the information published by the U. S. National Toxicology Program (NTP) that consisted of data from several mutagenicity studies and two carcinogenicity studies in rodents via the inhalational route of administration. Information was sent to the members of the EWG for their analysis.

Animal Toxicity

Genetic toxicology studies were conducted in Salmonella typhimurium, Chinese hamster ovary cells, Drosophila melanogaster, mouse bone marrow cells and mouse peripheral blood cells. The *in vitro* studies were conducted with and without exogenous metabolic activation from induced S9 liver enzymes. With the exception of an equivocal small increase above baseline in male mouse erythrocytes, no positive findings were found in any of the genetic toxicology studies.

Groups of 50 male and 50 female rats were exposed to 0, 200, 600, or 1,800 ppm tetrahydrofuran by inhalation, 6 hours per day, 5 days per week, for 105 weeks. Identical exposures were given to groups of 50 male and 50 female mice. Under the conditions of the studies, there was some evidence of carcinogenic activity of THF in male rats due to increased incidences of adenoma or carcinoma (combined) of the kidney. There was clear evidence of carcinogenic activity of THF in female mice due to increased incidences of hepatocellular adenomas and carcinomas. No evidence for carcinogenicity was found in female rats and male mice.

Using the lowest THF exposure in the most sensitive specie, the male rat at 200 ppm was used for the PDE calculation.

$$200\ \text{ppm} = \frac{200 \text{ x } 72.10}{24.45} = 589.8\ \text{mg/m}^3 = 0.59\ \text{mg/L}$$

$$\text{For continuous dosing} = \frac{0.59 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.105\ \text{mg/L}$$

$$\text{Daily dose} = \frac{0.105 \text{ x } 290}{0.425} = 71.65\ \text{mg/kg}$$

$$\text{PDE} = \frac{71.65 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x } 1} = 7.165\ \text{mg/day} = \mathbf{7.2\ mg/day}$$

$$\text{Limit} = \frac{7.2 \text{ x } 1000}{10} = \mathbf{720\ ppm}$$

Conclusion:

The former PDE for this solvent was greater than 50 mg/day (121 mg/day) and THF was placed in Class 3. The newly calculated PDE for tetrahydrofuran based upon chronic toxicity/carcinogenicity data is 7.2 mg/day, therefore, **it is recommended that Tetrahydrofuran be placed into Class 2** in Table 2 in the ICH Impurities: Residual Solvents Guideline. This is also the appropriate Class for THF because this Class contains those solvents that are non-genotoxic carcinogens and THF has been demonstrated to be a non-genotoxic carcinogen in rodents.

PART III:
IMPURITIES : RESIDUAL SOLVENTS (MAINTENANCE)
PDE FOR N-METHYLPYRROLIDONE (NMP)
ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 12 September 2002 and incorporated into the core Guideline in November 2005, this Guideline is recommended for adoption to the three regulatory parties to ICH

(Two mistyping corrections in the first calculation formula have been given on October 28, 2002 – this version is corrected)

The ICH Q3C guidance reached *Step 5* in December of 1997. It had been agreed by the members of the Expert Working Group (EWG) that the permissible daily exposure (PDE) could be modified if reliable and more relevant toxicity data was brought to the attention of the group. In 1999, a maintenance agreement was instituted and a Maintenance EWG was formed. The agreement provided for the re-visitation of solvent PDEs and allowed for minor changes to the guidance that included the existing PDEs. It was also agreed that new solvents and PDEs could be added based upon adequate toxicity data.

The EWG received new toxicity data for the solvent N-methylpyrrolidone late last year. It had been provided to the FDA by the NMP Producers Group. It was a 2-year chronic feeding study in rats performed by E.I. Dupont de Nemours & Co (unpublished data). The data was sent to the members of the EWG for their analysis. At the time, that data appeared to be the best available upon which to make a recommendation to the Steering Committee regarding a change in the status of NMP. At the last ICH meeting, February 28 to March 2, 2000, I briefed the Steering Committee on the results of the EWG's analysis and its consensus decision. The consensus was to remove NMP from Class 2 (PDE of 48.4 mg/day) and place it into Class 3 with a new PDE of 207 mg/day. Shortly thereafter, members of the EWG provided additional comment and data from which lower PDEs could be determined. The following paragraphs contain an analysis of an appropriate and more sensitive study from which to calculate a new PDE.

Animal Toxicity

The following paper was used for the calculation of the PDE for NMP:

"Effects Of Prenatal Exposure To N-Methylpyrrolidone On Postnatal Development And Behaviour In Rats", Hass U. et al., Neurotoxicol. Teratol.: 1994, 16, (3), 241-249.

Wistar rats were exposed by inhalation to 150ppm NMP for 6 hours/day, daily from days 7-20 of gestation and were then allowed to litter. No maternal toxicity was detected and litter size was unaffected by treatment. No physical abnormalities were described. The offspring were reduced in weight, the difference being statistically significant up to week 5 after birth. Pre-weaning development was impaired as was higher cognitive function related to solving of difficult tasks. Basal function of the CNS was normal and there were no effects on learning of low grade tasks. A NOEL was not established.

$$150 \text{ ppm} = \frac{150 \text{ x } 99.13}{24.45} = 608.16 \text{ mg/m}^3 = 0.608 \text{ mg/L}$$

$$\text{For continuous dosing} = \frac{0.608 \text{ x } 6}{24} = 0.152 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.152 \text{ x } 290}{0.33} = 133.58 \text{ mg/kg}$$

$$\text{PDE} = \frac{133.58 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 5 \text{ x } 5} = \mathbf{5.3 \text{ mg/day}}$$

$$\text{Limit} = \frac{5.3 \text{ x } 1000}{10} = \mathbf{530 \text{ ppm}}$$

Conclusion:

This study was chosen because of the toxicity endpoint that was seen, that is, the effect of the solvent on the function of the developing nervous system in utero. This is a potentially serious toxicity since we do not know if it is a permanent effect or if it is reversible. We are not sure if this delayed development could be due to the lower body weight of the pups. However, the EWG has decided to be cautious in its interpretation and in its safety decision.

The EWG members thus recommend that **N-methylpyrrolidone should be kept in Class 2** in Table 2 in the ICH Impurities: Residual Solvents Guideline. A new PDE and limit as described above should also be declared for this solvent. Class 2 contains those solvents that have significant toxicities such as neurotoxicity, non-genotoxic carcinogenicity, teratogenicity etc., and should be limited in their use up to the PDE limits listed in the table.

PART IV:
IMPURITIES : RESIDUAL SOLVENTS (MAINTENANCE)
PDE FOR CUMENE

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process and incorporated into the core Guideline on 4 February 2011, this Guideline is recommended for adoption to the three regulatory parties to ICH

Introduction

Cumene [synonyms: Cumol; isopropylbenzene; isopropylbenzol; (1-methyl/ethyl)benzene; 2-phenylpropane] is listed in the ICH Q3C guideline in Class 3, i.e., as a solvent with low toxicity. A summary of the toxicity data used by the EWG to establish a Permitted Daily Exposure (PDE) value for cumene at the time when the ICH Q3C guideline was signed off at *Step 2* in November 1996 is published in Connelly et al. (1).

According to this report from the EWG no data from carcinogenicity studies with cumene were available. Regarding genotoxicity data cumene was reported negative in an Ames test and in *Saccaromyces cerevisiae* and positive in *in vitro* UDS and cell transformation assays using mouse embryo cells. Calculation of a PDE value was based on a rat toxicity study published in 1956. Female Wistar rats were given cumene at doses of 154, 462 and 769 mg/kg by gavage 5 days/week for 6 months. No histopathological changes but slight increases in kidney weights at the two higher doses were observed suggesting a NOEL of 154 mg/kg. It was concluded that the PDE for cumene is 55.0 mg/day i.e., cumene is a solvent with low toxicity to be listed in Class 3. (1)

Meanwhile new toxicity data have been published including results from NTP 2-year inhalation studies showing that cumene is carcinogenic in rodents. (2) A reappraisal of the PDE value of cumene according to the maintenance agreement from 1999 is therefore initiated. For establishing a revised PDE value in this document the standard approaches (modifying factors, concentration conversion from ppm to mg/L, values for physiological factors) as described in detail in Connelly et al. (1) were used.

Genotoxicity

Cumene was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535, when tested with and without liver S9 activation enzymes. Cumene induced small, but significant, increases in micronucleated polychromatic erythrocytes in bone marrow of male rats treated by intraperitoneal injection. In contrast, no increase in micronucleated erythrocytes was observed in peripheral blood of male (up to 1000 ppm) or female (up to 500 ppm) mice exposed to cumene by inhalation for 3 months. (2)

p53 and K-*ras* mutations were found in 52% and 87% of lung neoplasms in exposed mice compared to 0% and 14% in the chamber controls, respectively. This pattern of mutations identified in the lung tumors suggests that DNA damage and genomic instability may be contributing factors to the development of lung cancer in mice. (3) However, the overall genotoxic profile does not provide sufficient evidence for a direct mutagenic mode of action of cumene or its metabolites as the primary cause in tumorigenesis. (2)

Carcinogenicity

F344 rats were exposed to concentrations of 250, 500, or 1000 ppm of cumene in air by inhalation 6h/day, 5 days/week for 2 years. Increased incidences of respiratory epithelial adenoma in the nose and renal tubule adenoma or carcinoma (combined) in males at all dose levels. Increased incidences of respiratory epithelium adenoma in the nose in females at all dose levels. (2)

Molecular weight of cumene: 120.19

LOEL 250 ppm (a NOEL for carcinogenic effects was not established)

$$250\ \text{ppm} = \frac{250 \text{ x } 120.19}{24.45} = 1229\ \text{mg/m}^3 = 1.23\ \text{mg/l}$$

$$\text{For continuous dosing} = \frac{1.23 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.22\ \text{mg/l}$$

$$\text{Daily dose} = \frac{0.22\ \text{mg l}^{-1} \text{ x } 290\ \text{l day}^{-1}}{0.425\ \text{kg}} = 150\ \text{mg/kg/day}$$

Rat respiratory volume: 290 l day^{-1}

Rat body weight: 0.425 kg

$$PDE = \frac{150 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x } 10} = 1.50\ \text{mg/day}$$

F1 = 5 to account for extrapolation from rats to humans

F2 = 10 to account for differences between individual humans

F3 = 1 because long duration of treatment (105 weeks)

F4 = 10 because oncogenic effect was reported

F5 = 10 because a NOEL was not established

$$\text{Limit} = \frac{1.5 \text{ x } 1000}{10} = 150\ \text{ppm}$$

B6C3F1 mice were exposed to concentrations of 125, 250, or 500 ppm (females) or 250, 500, or 1000 ppm (males) of cumene in air by inhalation 6h/day, 5 days/week for 2 years. Increased incidences of alveolar/bronchiolar neoplasms in males and females at all dose levels. Incidences of hepatocellular adenoma or carcinoma (combined) showed a dose-related increase in female mice. (2)

LOEL 125 ppm (female mice)

$$125\,\text{ppm} = \frac{125 \text{ x } 120.19}{24.45} = 614\,\text{mg/m}^3 = 0.61\,\text{mg/l}$$

$$\text{For continuous dosing} = \frac{0.61 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.11\,\text{mg/l}$$

$$\text{Daily dose} = \frac{0.11\,\text{mg l}^{-1} \text{ x } 43\,\text{l day}^{-1}}{0.028\,\text{kg}} = 169\,\text{mg/kg/day}$$

Mouse respiratory volume: 43 l day^{-1}

Mouse body weight: 0.028 kg

$$PDE = \frac{169 \text{ x } 50}{12 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x } 10} = 0.70\,\text{mg/day}$$

F1 = 12 to account for extrapolation from mice to humans

F2 = 10 to account for differences between individual humans

F3 = 1 because long duration of treatment (105 weeks)

F4 = 10 because oncogenic effect was reported

F5 = 10 because a NOEL was not established

$$\text{Limit} = \frac{0.7 \text{ x } 1000}{10} = 70\,\text{ppm}$$

Conclusion

The main carcinogenic effects in the rodent studies can be related to the inhalation route of administration (respiratory and olfactory tissues) and may therefore not be relevant for a residual solvent in (mainly) orally applied pharmaceuticals. However, systemic carcinogenic effects were also reported (kidney in male rats, liver in female mice) and the use of the NTP study data for calculation of a PDE is therefore considered appropriate.

The former PDE for this solvent was greater than 50 mg/day (55 mg/day) and cumene was placed in Class 3. The newly calculated PDE for cumene based upon carcinogenicity data is 0.7 mg/day, therefore, **it is recommended that cumene be placed into Class 2** in Table 2 in the ICH Impurities: Residual Solvents Guideline.

References

1. Connelly JC, Hasegawa R, McArdle JV, Tucker ML. ICH Guideline Residual Solvents. Pharmeuropa (Suppl) 1997;9:57.
2. Toxicology and Carcinogenesis Studies of Cumene (CAS No. 98-82-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Natl Toxicol Program Tech Rep Ser 2009;542;NIH 09-5885.
3. Hong HHL, Ton TVT, Kim Y, Wakamatsu N, Clayton NP, Chan PC et al. Genetic Alterations in K-*ras* and *p53* Cancer Genes in Lung Neoplasms from B6C3F1 Mice Exposed to Cumene. Toxicol Pathol, 2008;36:720-6.

PART V:
IMPURITIES : RESIDUAL SOLVENTS (MAINTENANCE)
PDE FOR TRIETHYLAMINE AND PDE OF METHYLISOBUTYLKETONE

ICH Harmonised Guideline

Having reached *Step 4* of the ICH Process and incorporated into the core Guideline on 9 November 2016 this Guideline is recommended for adoption to the regulatory parties to ICH

TRIETHYLAMINE

Introduction

Triethylamine (TEA) is used as catalytic solvent in chemical synthesis (1,2). It is a colourless liquid that is soluble in water, ethanol, carbon tetrachloride, and ethyl ether, and very soluble in acetone, benzene, and chloroform. TEA has a vapour pressure of 54 mmHg (20°C), and has been reported to be irritating to the lung and nasal passage with strong ammoniac odour (2,3).

Data from human studies show that TEA is easily absorbed *via* the oral or inhalation route and is rapidly excreted, mainly in the urine, as the parent compound and/or its *N*-oxide (4-6).

In studies in human volunteers, exposures of more than 2.5 ppm (10 mg/m^3) caused transient visual disturbance (4,7) due to a locally induced cornea swelling; no systemic effects were observed at the exposures which showed the cornea effect. The odour thresholds ranged from 0.0022 to 0.48 mg/m^3 (8-10).

Genotoxicity

In an Ames test TEA did not induce mutations in standard Salmonella strains with or without metabolic activation (11). TEA did not induce sister chromatid exchanges in Chinese hamster ovary cells with or without metabolic activation (12). In an *in vivo* study, TEA induced aneuploidy but was not clastogenic in the bone marrow of rats exposed to 1 mg/m^3 (0.25 ppm) and 10 mg/m^3 (2.5 ppm) TEA *via* continuous inhalation for 30 or 90 days (13). The weak aneugenic effect was observed at the low dose and early time point only; due to study deficiencies the relevance of this finding is highly questionable. Overall, the available data do not provide evidence for a relevant genotoxic potential of TEA.

Carcinogenicity

No data available.

Reproductive toxicity

No reliable information about reproductive toxicity is available. A three-generation reproductive study in which rats (10/sex/group) were administered 0, 2, or 200 ppm (c.a. 0, 0.14 or 14 mg/kg/day) TEA in drinking water was cited in the United States Environmental Protection Agency (US EPA) Integrated Risk Information System assessment review (14). The high dose was increased to 500 ppm in the third generation due to a lack of observed symptoms. No apparent effects occurred at 200 ppm through two generations. However, due to deficiencies in end-points measured the study data were disregarded from determining a Permitted Daily Exposure (PDE).

Repeated dose toxicity

A sub-chronic inhalation study (similar to Organisation for Economic Cooperation and Development [OECD] Test Guideline 413 and OECD Test Guideline 452) in rats is considered to be the most relevant published animal study for deriving a PDE. F344 rats (50 rats/group/sex) were exposed by whole body inhalation at concentrations of 0, 25, or 247 ppm (0, 0.10 or 1.02 mg/L) for 6 hours/day, 5 days/week for 28 weeks (15). No statistically significant treatment-related systemic effects were observed at all dose groups. Body weight gain was not statistically affected, although a slight dose-related decrease of body weight in male rats was observed. The No Observed Effect Level (NOEL) of this study was 247 ppm.

Molecular weight of TEA: 101.19 g/mol

NOEL 247 ppm

$$247 \text{ ppm} = \frac{247 \text{ x } 101.19}{24.45} = 1022.2 \text{ mg/m}^3 = 1.022 \text{ mg/L}$$

$$\text{For continuous dosing} = \frac{1.022 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.183 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.183 \text{mg L}^{-1} \text{ x } 290 \text{ L day}^{-1}}{0.425 \text{ kg}} = 124.9 \text{ mg/kg/day}$$

Rat respiratory volume: 290 L day^{-1}

Rat body weight: 0.425 kg

$$PDE = \frac{124.9 \text{ x } 50}{5 \text{ x } 10 \text{ x } 2 \text{ x } 1 \text{ x } 1} = 62.5 \text{ mg/day}$$

F1 = 5 to account for extrapolation from rats to humans

F2 = 10 to account for differences between individual humans

F3 = 2 because long duration of treatment (28 weeks)

F4 = 1 because no severe effects were observed

F5 = 1 because a NOEL was established

$$\text{Limit} = \frac{62.5 \text{ x } 1000}{10} = 6250 \text{ ppm}$$

Due to obvious study deficiencies other published animal toxicity data were disregarded from determining a PDE.

Conclusion

The calculated PDE for TEA based upon the NOEL of the rat sub-chronic inhalation study is 62.5 mg/day. Since the proposed PDE is greater than 50 mg/day it is recommended that TEA be placed into Class 3 ("solvents with low toxic potential") in Table 3 in the ICH Impurities: Residual Solvents Guideline.

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METHYLISOBUTYLKETONE

Introduction

Methylisobutylketone (MIBK) is listed in the ICH Q3C parent Guideline of 1997 in Class 3, i.e., as a solvent with low toxicity based on a review of toxicity data available at that time resulting in a Permitted Daily Exposure (PDE) value for MIBK of 100 mg/day (1). Due to new toxicity data including results from National Toxicology Program (NTP) 2-year rat and mouse inhalation carcinogenicity studies and published studies on reproductive and developmental toxicity the Expert Working Group has re-evaluated the PDE value of MIBK.

Genotoxicity

No additional information about genotoxicity has been reported, since the last assessment was conducted in 1997. The available data suggest that MIBK is not genotoxic.

Carcinogenicity

MIBK has been studied by NTP in 2-year rat and mouse inhalation studies. F344/N rats and B6C3F1 mice (50 animals/sex/group) were exposed to MIBK at concentrations of 0, 450, 900, or 1800 ppm by inhalation, 6 hours per day, 5 days per week for two years. Survival was decreased in male rats at 1800 ppm (4). Body weight gains were decreased in male rats at 900 and 1800 ppm and in female mice at 1800 ppm. The primary targets of MIBK toxicity and carcinogenicity were the kidney in rats and the liver in mice. The NTP Technical Report concluded that there was some evidence of carcinogenic activity of MIBK in rats and mice (4,5). Based on these NTP data, IARC has classified MIBK as a group 2B carcinogen ("possibly carcinogenic to humans") (6).

In the rat NTP study, MIBK caused an increase in Chronic Progressive Nephropathy (CPN) and a slight increase in the incidences of renal tubule adenoma and carcinomas in males at the highest dose. Further mechanistic studies provide clear evidence that the renal tubular tumors in male rats are most likely caused through the well-known male rat specific α2u-nephropathy-mediated mode of action, which is considered to be without relevance to humans (7). Exacerbated CPN was also observed in female rats (increases in the incidence of CPN in all exposure concentrations and in the severity at 1800 ppm) the human relevance of which is currently unclear. Increases in mononuclear cell leukemias in male rats at 1800 ppm and the occurrence of two renal mesenchymal tumors (very rare tumor, not observed in NTP historical control animals) in female rats at 1800 ppm were findings with uncertain relationship to MIBK exposure (5).

From the results of the rat carcinogenicity study with MIBK, PDEs are calculated based on two different scenarios:

(i) tumor findings in male and female rats are not treatment-related and/or not relevant to humans and therefore the CPN in female rats observed at the lowest dose (LOEL[12] = 450 ppm) is used for PDE calculation.

or

(ii) relationship to MIBK exposure and relevance of rat tumor findings at 1800 ppm in males (mononuclear cell leukemias) and/or females (renal mesenchymal tumors) to humans cannot be excluded; the NOEL for tumors of 900 ppm is used for PDE calculation.

[12] Lowest Observed Effect Level

Molecular weight of MIBK: 100.16 g/mol

Scenario 1: $LOEL_{(CPN)}$ 450 ppm (rat)

$$450 \text{ ppm} = \frac{450 \text{ x } 100.16}{24.45} = 1843 \text{ mg/m}^3 = 1.843 \text{ mg/L}$$

$$\text{For continuous dosing} = \frac{1.843 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.329 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.329 \text{ mg L}^{-1} \text{ x } 290 \text{ L day}^{-1}}{0.425 \text{ kg}} = 225 \text{ mg/kg/day}$$

Rat respiratory volume: 290 L day^{-1}

Rat body weight: 0.425 kg

$$PDE = \frac{225 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x } 5} = 45 \text{ mg/day}$$

F1 = 5 to account for extrapolation from rats to humans

F2 = 10 to account for differences between individual humans

F3 = 1 because long duration of treatment (2 years)

F4 = 1 low severity of effect (CPN in females) with unclear relevance for humans

F5 = 5 because a NOEL for CPN was not established

$$\text{Limit} = \frac{45 \text{ x } 1000}{10} = 4500 \text{ ppm}$$

Scenario 2: $NOEL_{(tumor)}$ 900 ppm (rat)

$$900 \text{ ppm} = \frac{900 \text{ x } 100.16}{24.45} = 3687 \text{ mg/m}^3 = 3.687 \text{ mg/L}$$

$$\text{For continuous dosing} = \frac{3.687 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.658 \text{ mg/L}$$

$$\text{Daily dose} = \frac{0.658 \text{ mg L}^{-1} \text{ x } 290 \text{ L day}^{-1}}{0.425 \text{ kg}} = 449 \text{ mg/kg/day}$$

Rat respiratory volume: 290 L day^{-1}

Rat body weight: 0.425 kg

$$PDE = \frac{449 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x } 1} = 44.9 \text{ mg/day}$$

F1 = 5 to account for extrapolation from rats to humans

F2 = 10 to account for differences between individual humans

F3 = 1 because long duration of treatment (2 years)

F4 = 10 severity of endpoint (cancer)

F5 = 1 because a NOEL was established

$$\text{Limit} = \frac{44.9 \text{ x } 1000}{10} = 4490 \text{ ppm}$$

In the mouse study, MIBK increased the incidence of hepatocellular adenomas, and adenoma or carcinoma (combined) in male and female mice exposed to 1800 ppm. Further mechanistic studies provide clear evidence for a constitutive androstane receptor (CAR)-mediated mode of action (MOA) for the mouse liver tumors (8). Since this MOA has been identified as not relevant for humans (9), no PDE calculation was done based on the mouse 2-year study data.

Reproductive and developmental toxicity

In a developmental toxicity study, pregnant F-344 rats were exposed to MIBK by inhalation at doses 0, 300, 1000, or 3000 ppm, 6 hours/day on gestational day 6 through 15. Some fetotoxicities (reduced fetal body weight and reductions in skeletal ossification) observed at 3000 ppm are considered to be secondary to maternal toxicities. There was no maternal, embryo, or fetal toxicity at 1000 ppm (2).

In a two-generation reproduction study, SD rats were exposed to MIBK *via* whole-body inhalation at concentrations of 0, 500, 1000, or 2000 ppm, 6 hours/day, for 70 days covering the period prior to mating of F0 generation through the lactation period of F2 generation. The NOEL for reproductive effects was 2000 ppm, the highest concentration tested; the NOEL for neonatal toxicity was 1000 ppm, based on acute Central Nervous System depressive effects (3).

Conclusion

The former PDE of MIBK was greater than 50 mg/day (100 mg/day) and the solvent was placed in Class 3. The newly calculated PDE of MIBK is based upon the NOEL for tumors in male and female rats and the LOEL for chronic progressive nephropathy in female rats from the NTP 2-year inhalation study; in both cases a PDE of 45 mg/day was calculated. Therefore, it is recommended that MIBK be placed into Class 2 in Table 2 in the ICH Impurities: Residual Solvents Guideline.

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PART VI:
IMPURITIES : RESIDUAL SOLVENTS (MAINTENANCE)
PDE FOR 2-METHYLTETRAHYDROFURAN, CYCLOPENTYL METHYL ETHER, AND TERTIARY-BUTYL ALCOHOL

ICH Harmonised Guideline

2-METHYLTETRAHYDROFURAN

Introduction

2-Methyltetrahydrofuran (2-MTHF, synonyms: 2-methyloxolane, tetrahydrosylvan; tetrahydro-2-methylfuran; CAS Number 96-47-9) is a colourless, volatile liquid with ether-like odour. 2-MTHF is an organic solvent usually synthesized as a racemic mixture consisting of two enantiomeric forms ((S)+ and (R)-). Solubility in water is limited and decreases with increasing temperature. It has a vapour pressure of 102 millimeters of mercury (mmHg) (20°C) (1). For practical reasons, 2-MTHF is a racemic mixture when used as a solvent in synthetic processes.

2-MTHF is increasingly used as a catalytic solvent in exchange of tetrahydrofuran and is much less miscible with water compared to tetrahydrofuran.

Genotoxicity

2-MTHF was not mutagenic in the Ames bacterial reverse mutation assay with *Salmonella typhimurium* (3) and *Escherichia coli* WP2 *uvrA* (2). 2-MTHF was also tested *in vitro* in a L5178Y mouse lymphoma cell TK+/- assay (3), in a chromosome aberration assay in human peripheral blood lymphocytes (2), and *in vivo* in a bone marrow micronucleus test integrated into a 3-month oral repeated-dose toxicity study in rats (2). All test results were negative except for the mouse lymphoma assay in the presence of S9, which was considered inconclusive without further explanation (3). In conclusion, there is no evidence that 2-MTHF is genotoxic.

Carcinogenicity

No data for 2-MTHF are available.

Reproductive and developmental toxicity

2-MTHF was tested in a GLP-compliant prenatal developmental toxicity study according to OECD TG414 in rats with doses of 100, 300 and 1,000 milligrams per kilogram per day (mg/kg/day) (4). At 1,000 mg/kg/day, 2-MTHF caused slightly reduced maternal weight gain, slightly lower gravid uterus weight, and marginally reduced foetal body weight. Only slight effects on foetal growth were observed and overall foetal survival and development were considered unaffected at the highest dose. The no-observed-adverse-effect level (NOAEL) was considered 1,000 mg/kg/day. However, as detailed toxicity information is not available, this study was not used to support the calculation of a permitted daily exposure (PDE). In an acute embryo toxicity and teratogenicity test in zebrafish, 2-MTHF was tested at concentrations ranging from 860 – 8,600 milligrams/liter (mg/L) (5). Acute embryo toxicity was observed for 2-MTHF at a nominal LC_{50} value of 2,980 mg/L. Sublethal effects were also observed, such as an increase in oedema at nominal concentrations ≥ 1,720 mg/L, as well as an increased number of embryos without detectable blood circulation and insufficient pigmentation at a nominal concentration of 2,580 mg/L. Teratogenic effects were not observed with 2-MTHF in this assay.

Repeated-dose toxicity

Two 3-month oral repeated-dose toxicity studies in Crl:CD (SD) rats have been described with 2-MTHF racemate; one without a recovery period (2) and one with a 1-month recovery period (6). The top dose in the first study was 26 mg/kg/day (2), and in the second study 1,000 mg/kg/day (6). 2-MTHF treatment-related observations were not seen in the first study (2). In the second study, groups of 10 male and 10 female rats per dose group were treated with doses of 80, 250, 500, and 1,000 mg/kg/day (6). The 1-month treatment-free recovery period included 5 animals/sex for the control and the high-dose groups. Treatment-related observations were generally seen at doses ≥ 500 mg/kg/day. Besides slight effects on kidney weights (increased at ≥ 500 mg/kg/day), blood cholesterol (increased at 1,000 mg/kg/day) and prothrombin time (decreased at ≥ 500 mg/kg/day), the only test article-related microscopic observation was hepatocellular centrilobular hypertrophy at 1,000 mg/kg/day. However, no effects were observed in the recovery group and the observed effects can therefore be regarded as completely reversible. The no-observed-effect level (NOEL) in the second study was considered 250 mg/kg/day.

The NOEL of 250 mg/kg/day was used in the PDE calculation:

$$PDE = \frac{250 \text{ x } 50}{5 \text{ x } 10 \text{ x } 5 \text{ x } 1 \text{ x } 1} = 50 \text{ mg/day}$$

F1 = 5 to account for extrapolation from rats to humans

F2 = 10 to account for differences between individual humans

F3 = 5 for a 3-month study in rodents

F4 = 1 because no severe effects were observed

F5 = 1 because a NOEL was established

Conclusion

The calculated PDE for 2-MTHF is 50 milligrams per day (mg/day) based upon the NOEL of the rat sub-chronic oral study. Since the PDE is 50 mg/day, it is recommended that 2-MTHF be placed into class 3 “Solvents With Low Toxic Potential” in Table 3 in the International Council for Harmonisation (ICH) Q3C guideline on Impurities: Residual Solvents.

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CYCLOPENTYL METHYL ETHER

Introduction

Cyclopentyl methyl ether (CPME: CAS Number 5614-37-9) is used in pharmaceutical chemical development as an alternative to its more common analogues, such as tetrahydrofuran and tert-butyl methyl ether (1,2).

The vapour pressure of CPME is 44.9 mmHg at 25°C, the Log P_{ow} is 1.59, and the water solubility is 1.1 grams per 100 grams (23 °C) (3,4).

CPME is classified as an irritant to skin (H315) and eye (H319) in accordance with EC No 1272/2008, in the Globally Harmonized System of Classification and Labelling of Chemicals. CPME did not show the potential to induce skin sensitization in the local lymph node assay. In rats, LD_{50} for acute oral exposure is 1,000–2,000 mg/kg, for dermal exposure it is greater than 2,000 mg/kg, and for inhalation exposure it is greater than 21.5 mg/L. No human toxicity data have been reported (2).

Genotoxicity

The results of genotoxicity tests have been reported (1,2). CPME was not mutagenic in the Ames bacterial reverse mutation assays in *S. typhimurium* test strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* with and without metabolic activation at concentrations up to 5,710 micrograms per plate (1) and 5,000 micrograms per plate (2). Negative results were also obtained in *in vitro* mammalian chromosome aberration tests in human lymphocytes at concentrations up to 1.1 milligrams per millilitre (mg/mL) and in Chinese hamster lung cells at concentrations up to 1.0 mg/mL (2). An *in vivo* rat micronucleus test integrated in a 3-month oral repeated-dose study up to a dose of 31 mg/kg/day (1) and an *in vivo* mammalian erythrocyte micronucleus test in CD-1 mice at single oral doses up to 2,000 mg/kg (2) also did not indicate any genotoxic potential. In conclusion, there is no evidence that CPME is genotoxic.

Carcinogenicity

No data are available.

Reproductive and developmental toxicity

In a two-generation reproductive toxicity study, CPME was administered to rats in drinking water at doses of 313, 1,250, or 5,000 mg/mL (5). Other than decreased body weights of pups in the F1 generation and F2 generation which were observed at the highest dose, no other significant changes in reproductive parameters were reported. The no-observed-adverse-effect level (NOAEL) of this study was estimated to be 193.45 mg/kg/day (1,250 mg/L in drinking water). However, as detailed toxicity information from this study is not available, this study was not used to support the calculation of a PDE.

Repeated-dose toxicity

CPME was studied in two oral and one inhalation repeated-dose studies in rats.

In a 28-day study with a 14-day recovery period, Crj: Crl:CD(SD) rats were administered CPME by oral gavage at 15, 150, or 700 mg/kg/day in corn oil (2,6). Six unscheduled deaths occurred in males at 700 mg/kg/day between days 12 and 15 of treatment and were attributed to poor clinical conditions. Salivation was commonly observed in males and females at 700 mg/kg/day. Salivation occurred twice in one male at 150 mg/kg/day; however, this finding was not considered adverse. Decreased motor activity, piloerection, abnormal gait, tremors, convulsion, hunched posture, fast respiration, and thin appearance were observed in males at 700 mg/kg/day. Decreased body weight

gain was observed in females at 700 mg/kg/day. All clinical findings and changes in bodyweight gains resolved after the recovery period. There were no other toxicological effects of CPME in this study. The no-observed-effect level (NOEL) of this study was determined to be 150 mg/kg/day.

In a 90-day study, Sprague Dawley Crl:CD(SD) rats were administered up to 31 mg/kg/day CPME by oral gavage in corn oil (1). There were no CPME-related ante-mortem or post-mortem findings. Detailed information on the experimental design and study results, such as clinical signs, haematology, and blood chemistry findings, were not publicly available, although the authors considered the NOEL of this study to be 31 mg/kg/day. In another 90-day study, Sprague Dawley rats were administered up to 500 mg/kg/day CPME by oral gavage in water (7). The NOAEL of this study was estimated to be 32 mg/kg/day. However, as detailed toxicity information from this study is not publicly available and this study was not conducted under GLP, this study was not used to support the calculation of a PDE.

In a 90-day study with a 28-day recovery period, Crj: CD (SD) IGS rats were exposed to gaseous CPME up to 4 mg/L (6 hours/day, 5 days/week) by whole-body inhalation exposure (2). Toxic effects occurred at 4 mg/L and included clinical findings of salivation and nasal discharge, decreased body weights, increased levels of alanine aminotransferase and potassium (in males), increased absolute and body weight-relative kidney weight (in males), hyaline droplets in the proximal tubular epithelium of the kidney, and simple hyperplasia of the mucosal epithelium of the urinary bladder. All adverse effects were reversible following the recovery period. The NOEL of this study was determined to be 0.84 mg/L.

The most appropriate and well-documented study for CPME toxicity was the 28-day oral rat study. The PDE was calculated based on the identified NOEL of 150 mg/kg/day from this study.

$$PDE = \frac{150 \text{ x } 50}{5 \text{ x } 10 \text{ x } 10 \text{ x } 1 \text{ x } 1} = 15 \text{ mg/day}$$

F1 = 5 to account for extrapolation from rats to humans

F2 = 10 to account for differences between individual humans

F3 = 10 because duration of treatment was less than 3 months

F4 = 1 because no severe effects were observed

F5 = 1 because a NOEL was established

Limit = (15 x 1,000)/10 = 1,500 ppm

Conclusion

The calculated PDE for CPME is 15 mg/day based upon the NOEL from the 28-day oral toxicity study. Therefore, it is recommended that CPME be placed into class 2 “Solvents To Be Limited” in Table 2 in ICH Q3C Guideline.

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TERTIARY-BUTYL ALCOHOL

Introduction

Tertiary-butyl alcohol (*t*-Butyl alcohol, tert-butanol; TBA: CAS Number 75-65-0) is a tertiary aliphatic alcohol and is used for a variety of purposes including as an alcohol denaturant, a dehydration agent, and a solvent (1). TBA is soluble in water and has a vapour pressure of 31 mm Hg (20°C). TBA is rapidly absorbed following inhalation or ingestion, but poorly absorbed through skin (2).

The rat oral LD_{50} (lethal dose for 50% of animals, combined values for males and females) has been reported to be between 2,733 and 3,500 mg/kg body weight. The primary acute effects observed in animals are signs of alcoholic intoxication. Human clinical test data indicate that TBA is neither an irritant nor a sensitizer (3). Its potency for intoxication is approximately 1.5 times that of ethanol (4). Given its wide diversity of use, the potential for human exposure to TBA is high (5). The National Institute for Occupational Safety and Health indicates that TBA's use is widespread in the workplace (1). A Cosmetic Ingredient Review Expert Panel also concluded that TBA is safe as used in cosmetic products with concentrations ranging from 0.00001 to 0.3% (3).

Genotoxicity

TBA was not mutagenic in the Ames bacterial reverse mutation assay (6). The US National Toxicology Program (NTP) studies also showed TBA was not genotoxic *in vitro* with and without metabolic activation (S9) (mouse lymphoma cell mutation assay, chromosome aberrations, sister chromatid exchanges). *In vivo*, no increases in micronucleated erythrocytes were observed in peripheral blood samples from mice administered up to 40000 parts per million (ppm) TBA in drinking water for 13 weeks or up to 625 mg/kg administered by intraperitoneal injection 3 times at 24-hour intervals (6). In conclusion, there is no evidence that TBA is genotoxic (2).

Carcinogenicity

TBA was investigated by the NTP in two drinking water studies, one in F344/N rats and one in B6C3F1 mice (1,6). Both studies included 3 treatment groups (60 animals/sex/group; 50 animals/sex/group completed the study): in rats, doses of 85, 195, and 420 mg/kg/day in males and 175, 330, and 650 mg/kg/day in females; and in mice, doses of 535, 1,035, and 2,065 mg/kg/day in males and 510, 1,015, and 2,105 mg/kg/day in females) (1). Survival was decreased in high dose rats and high dose male mice. Final mean body weights were decreased in exposed male and high dose female rats and high dose female mice. The primary targets of TBA were the kidney (mineralization, hyperplasia, tumours) in male rats and the thyroid gland (follicular cell hyperplasia, tumours) and urinary bladder (inflammation and epithelial hyperplasia) in mice. The NTP Technical Report concluded that there was some evidence of carcinogenic activity in male rats based on increased incidences of renal tubule adenoma or carcinoma (combined) and in female mice based on increased incidences of follicular cell adenoma of the thyroid gland (6). There was no evidence of carcinogenicity in female rats and equivocal evidence in male mice.

In mice, the incidence of thyroid follicular cell adenoma was significantly increased in high dose females. These tumorigenic effects were associated with an increased incidence and severity of focal follicular cell hyperplasia of the thyroid gland in all TBA-treated groups of males and females (1,6). In contrast, no thyroid tumours were observed in an 18-month carcinogenicity study of methyl *tert*-butyl ether by the inhalation route in CD-1 mice (7). The systemic TBA exposure (as a metabolite of methyl *tert*-butyl ether) likely exceeded the exposure in the NTP study (2). However, differences in strain of mice (CD-1 versus B6C3F1) or route of administration may be responsible for the differences in response. In the absence of evidence suggesting direct thyroid toxicity, it was hypothesized that TBA induced thyroid tumours in the drinking water study through increased liver metabolism of thyroid hormones, triggering a compensatory increase in thyroid stimulating hormone production and, thus, thyroid follicular cell proliferation and

hyperplasia (2). Rodents are substantially more sensitive than humans to the development of thyroid follicular cell tumours in response to thyroid hormone imbalance. Thus, the dose response is non-linear, and tumours are not expected to occur in humans in the absence of altered thyroid hormone homeostasis (8,9). In partial agreement with the above hypothesis, TBA is an inducer of phase I and II liver enzymes following 14 days of oral exposure at doses less than or equal to those used in chronic studies, and TBA administration resulted in a small decrease in circulating thyroid hormones in B6C3F1 mice (10). However, no meaningful changes in thyroid stimulating hormone levels were observed in this study. A comprehensive review of the mouse carcinogenicity data concluded that, in the absence of meaningful effect on thyroid stimulating hormone and toxicity to the thyroid, the cause of the increase in either hyperplasia or adenoma incidence remains unclear (2). TBA administration also resulted in an increased incidence of chronic inflammation and hyperplasia of the transitional epithelium of the urinary bladder in high-dose males and females.

In rats, an increased incidence of renal tubule adenomas and carcinomas was observed in males exposed to TBA, but the increase was not dose-dependent. The evidence suggests that these tumours are due to a α2μ-globulin nephropathy-mediated mode of action. α2μ-Globulin nephropathy is a well-recognized sex- and species-specific mechanism of toxicity without relevance to humans (11,12). Foci of linear mineralization in the renal medulla, a lesion consistently reported as a long-term consequence of α2μ-globulin nephropathy, were observed in the high dose male rats (1,6). Further, TBA was shown to interact with α2μ, which explains the accumulation of α2μ in the male rat kidney (5). Although no significant neoplastic findings were observed in female rats, a dose-dependent increase in severity of nephropathy was observed at all TBA doses compared to control animals (average severity of 1.6, 1.9, 2.3, and 2.9; scale of 0–4); incidence ranged from 47–48 out of 50 animals in all groups. An increased incidence of transitional epithelial hyperplasia and suppurative inflammation at the two highest doses and renal tubule hyperplasia in a single high dose animal were also observed. The human relevance of the renal findings in female rats is currently unclear.

The 2-year carcinogenicity studies were considered the most relevant for calculation of the PDE for TBA. From the results of the rat and mouse carcinogenicity studies, PDEs were calculated based on two different scenarios:

(1) Renal lesions and tumour findings in male rats are not relevant to humans and, therefore, the increased severity in nephropathy observed in female rats at the lowest dose (lowest-observed-effect level (LOEL) = 175 mg/kg/day is used for the PDE calculation.

or

(2) Increased incidence of follicular cell hyperplasia in the thyroid of female mice at the lowest TBA dose (LOEL = 510 mg/kg/day) is used for the PDE calculation.

Scenario 1 (rat): $LOEL_{(nephropathy)}$ 175 mg/kg/day

$$PDE = \frac{175 \text{ x } 50}{5 \text{ x } 10 \text{ x} 1 \text{ x } 1 \text{ x } 5} = 35 \text{ mg/day}$$

F1 = 5 to account for extrapolation from rats to humans

F2 = 10 to account for differences between individual humans

F3 = 1 because long duration of treatment (2 years)

F4 = 1 due to similar severity of effect (nephropathy in females) at the low dose compared to control animals

F5 = 5 because a no-observed-effect level (NOEL) for nephropathy was not established

Limit = (35 x 1,000)/10 = 3,500 ppm

Scenario 2 (mouse): $LOEL_{(follicular\ cell\ hyperplasia)}$ 510 mg/kg/day

$$PDE = \frac{510 \text{ x } 50}{12 \text{ x}10 \text{ x}1 \text{ x}1 \text{ x } 5} = 42.5 \text{ mg/day}$$

F1 = 12 to account for extrapolation from mice to humans

F2 = 10 to account for differences between individual humans

F3 = 1 because long duration of treatment (2 years)

F4 = 1 because hyperplasia response was of minimal to mild average severity at all doses and thyroid tumours were not observed at the low dose

F5 = 5 because a NOEL for hyperplasia was not established

Limit = (42.5 x 1000)/10 = 4250 ppm

The ultimate PDE for TBA, calculated based on the identified LOEL of 175 mg/kg/day from the 2-year rat study, is 35 mg/day.

Reproductive and developmental toxicity

TBA has not been associated with induction of skeletal or visceral malformations in rats or mice but did induce developmental delays and intrauterine or prenatal mortality at doses of 1,000 mg/kg/day or greater (2).

In a reproduction/developmental toxicity screening study, TBA was administered to Sprague-Dawley rats (12/sex/group) by oral gavage at dose levels of 0, 64, 160, 400, and 1,000 mg/kg/day for up to 63 days in males and from 4 weeks before mating until postnatal day 20 in females (13). There were no adverse effects on any reproductive parameters, including mating index, fertility index, pregnancy index, or gestation index. For dams receiving 1,000 mg/kg/day TBA through gestation and lactation, there was a significant reduction in mean litter size, a decrease in the number of live born per pregnancy, an increase in the number of stillborn pups, increased pup mortality up to postnatal day 4, and a decrease in mean pup body weight at birth, which continued to weaning. Parental toxicity (transient central nervous system effects, reduced body weight and food consumption) was observed at doses of 400 mg/kg or greater. The no-observed-adverse-effect level (NOAEL) for developmental/reproductive effects was identified as 400 mg/kg/day.

At a dose of 1,000 mg/kg/day, mild to moderate transient systemic toxicity was observed in both sexes in the parental generation including reversible central nervous system effects such as lethargy and ataxia, and reduced food consumption and weight gain. At 400 mg/kg/day, an

increased incidence of transient mild lethargy/ataxia in females was observed. The NOEL for parental toxicity was 160 mg/kg/day.

Repeated-dose toxicity

In a sub-chronic toxicity study, TBA was administered to F344/N rats (10/sex/dose) *ad libitum* in drinking water at dose levels of 0, 2.5, 5, 10, 20, and 40 mg/mL for 13 weeks (equivalent to 176, 353, 706, 1,412 and 2,824 mg/kg/day) (6). All high dose males and six high dose females died during the study. Nephropathy was the most sensitive effect observed in the study. An increase in severity of nephropathy was observed in the lower four dose groups in males when compared to control animals, as was the accumulation of hyaline droplets in the kidney at doses of 353, 706, and 1,412 mg/kg/day. The incidence of nephropathy in females at the highest three doses was significantly greater than that in the controls. Transitional epithelial hyperplasia and inflammation of the urinary bladder were observed at the two highest doses in males and in high dose females. Based on the nephropathy in male rats at the lowest dose, 176 mg/kg/day was considered the LOEL. As noted above, α2μ-globulin nephropathy is a well-recognized sex- and species-specific mechanism of toxicity without relevance to humans (11,12).

TBA was also administered to B6C3F1 mice (10/sex/dose) in drinking water for 13 weeks at the same concentrations provided to rats (doses equivalent to 446, 893, 1,786, 3,571, and 7,143 mg/kg/day) (6). Two high dose males and one high dose female died. The final mean body weights in males at the two highest doses and in females at the high dose were significantly lower than that in the control animals. Transitional epithelial hyperplasia and inflammation were observed in the urinary bladder of the same groups. A NOEL of 1,786 mg/kg/day was identified (6).

Conclusion

The calculated PDE for TBA is 35 mg/day based upon the LOEL for nephropathy in females from the 2-year rat carcinogenicity study. It is recommended that TBA be placed into class 2, “Solvents To Be Limited” in Table 2 in ICH Q3C Guideline.

References

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