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ICH guideline Q3C (R7) on impurities: guideline for residual solvents

Step 5

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Document History

First Codification	History	Date	New Codification

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
Q3C	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	17 July 1997	Q3C

Revision of the PDE information for THF contained in the Parent Guideline

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	in Q3C(R1)
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	in Q3C(R1)

Revision of PDE information for NMP contained in the Parent Guideline

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	in Q3C(R2)
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	in Q3C(R2)
Q3C(M) for NMP	Corrigendum to calculation formula approved by the Steering Committee.	28 October 2002	in Q3C(R3)
Q3C, Q3C(M) for THF and Q3C(M) for NMP	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	Q3C(R3)

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	Q3C(R4)

Revision of PDE information for Cumene contained in the Parent Guideline

PDE for Cumene	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	in Q3C(R5)

Current *Step 4* version

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	Q3C(R5)

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

PDE for Triethylamine and Methylisobutylketone	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	in Q3C(R6)
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	Q3C(R6)

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.	5 September 2018	in Q3C(R7)

Q3C (R7): Impurities: guideline for residual solvents

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Part I

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.

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

Solvent	Concentration limit (ppm)	Concern
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
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	3.1	310
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[2]	45	4500
N-Methylpyrrolidone[3]	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200

[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 22-25).
[2] 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 26-34).
[3] 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 20-21).

Solvent	PDE (mg/day)	Concentration limit (ppm)
Sulfolane	1.6	160
Tetrahydrofuran[4]	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	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	Triethylamine[5]

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

[4] 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 18-19).
[5] 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 26-34).

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	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

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.

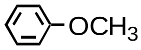
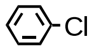
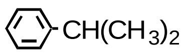
Strongly Suspected Human Carcinogen:

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

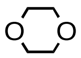
Teratogenicity:

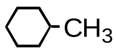
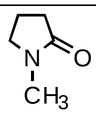
The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

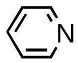
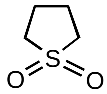
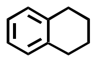
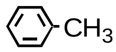
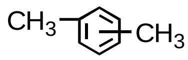
Appendix 1. List of solvents included in the guideline

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
Carbon tetrachloride	Tetrachloromethane	CCl4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	CHCl3	Class 2
Cumene[6]	Isopropylbenzene (1-Methyl)ethylbenzene		Class 2
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH2ClCH2Cl	Class 1

[6] 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 22-25).

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
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
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
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[7]	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
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

[7] 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 18-19).

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:

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

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 5. 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/m3. 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.

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

The relationship 1000 L = 1 m3 is used to convert to mg/ m3.

Part II: PDE for Tetrahydrofuran

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.

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

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

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

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

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

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

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: PDE for N-Methylpyrrolidone (NMP)

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.

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

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

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

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

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

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: PDE for Cumene

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)

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

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

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

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

Rat body weight: 0.425 kg

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

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

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

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)

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

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

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

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

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Part V: PDE for Triethylamine and PDE of Methylisobutylketone

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:

relevant to humans and therefore the CPN in female rats observed at the lowest dose (LOEL[8] = 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.

Molecular weight of MIBK: 100.16 g/mol

[8] Lowest Observed Effect Level

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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