EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 23 July 2015
2 EMA/CHMP/ICH/82260/2006
3 Committee for Human Medicinal Products

4 Q3C (R6): Impurities: guideline for residual solvents

5 Step 2b

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 November 2015

6

7 The proposed guideline will replace 'ICH Q3C (R5) Guideline to include a PDE for triethylamine and
8 revise the PDE of methylisobutylketone due to new toxicity data'[1].

9

Comments should be provided using this template. The completed comments form should be sent to ich@ema.europa.eu

[1] If this supersedes a previous guideline – otherwise delete.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

10 Document History

First Codification	History	Date	New Codification Nov. 2005

11 **Parent Guideline: Impurities: Guideline for Residual Solvents**

Q3C	Approval by the CPMP under *Step 3* and release for public consultation.	November 1996	Q3C
Q3C	Approval by the CPMP under *Step 4* and release for information.	September 1997	Q3C

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

Q3C(M) for THF	Permitted Daily Exposure (PDE) for Tetrahydrofuran (THF): revision of PDE based on new toxicological data. Approval by CPMP of the new PDE for THF under *Step 3* and release for public consultation.	July 2000	in Q3C(R1)
Q3C(M) for THF	Approval by the CPMP under *Step 4* and release for information.	September 2002	in Q3C(R1)

13 **Revision of PDE information for NMP contained in the Parent Guideline**

Q3C(M) for NMP	Permitted Daily Exposure (PDE) for N-Methylpyrrolidone (NMP): revision of PDE based on new toxicological data. Approval by CPMP of the Revision under *Step 3* and release for public consultation.	July 2000	in Q3C(R2)
Q3C(M) for NMP	Approval by the CPMP under *Step 4* and release for information.	September 2002	in Q3C(R2)
Q3C(M) for NMP	Corrigendum to calculation formula approved by the CPMP.	November 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)

14 **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)

15 **Revision of PDE information for Cumene contained in the Parent Guideline**

PDE for Cumene	Permitted Daily Exposure (PDE) for Cumene: revision of PDE based on new toxicological data. Approval by CHMP under *Step 3* and release for public consultation.	June 2010	in Q3C(R5)
Q3C(R5)	Approval of the PDE for Cumene by CHMP under *Step 4* and release for information. 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.	March 2011	Q3C(R5)

16 **Current *Step 2b* version**

Q3C(R6)	Addition of PDE for triethylamine and revision of the PDE of methylisobutylketone due to new toxicity data. Approval by CHMP under *Step 2b* and release for public consultation.	July 2015	in Q3C(R6)

17

Q3C (R6): Impurities: guideline for residual solvents

Table of contents

1. Triethylamine

1.1. Introduction

Triethylamine 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. Triethylamine 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 triethylamine 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).

1.2. Genotoxicity

In an Ames test triethylamine did not induce mutations in standard Salmonella strains with or without metabolic activation (11). Triethylamine did not induce sister chromatid exchanges in Chinese hamster ovary cells with or without metabolic activation (12). In an *in vivo* study, triethylamine 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) triethylamine 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.

1.3. Carcinogenicity

No data available.

1.4. 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, 1.4 or 14 mg/kg/day) triethylamine in drinking water was cited in the U.S. 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 PDE.

1.5. Repeated dose toxicity

A sub-chronic inhalation study (similar to 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 NOEL of this study was 247 ppm.

Molecular weight of triethylamine: 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.

1.6. Conclusion

The calculated PDE for triethylamine 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 triethylamine be placed into Class 3 (“solvents with low toxic potential”) in Table 3 in the ICH Impurities: Residual Solvents Guideline.

1.7. References

Lide, D.R. CRC Handbook of Chemistry and Physics 86TH Edition 2005-2006. CRC Press, Taylor & Francis, Boca Raton, FL 2005, p. 3-498.

Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 14th Edition. John Wiley & Sons, Inc. New York, NY 2001., p. 1125.

OECD SIDS Initial Assessment Profile: Tertiary Amines. CoCAM 2, 17/04/2012, assessed. (available from the OECD Existing Chemicals Database (http://webnet.oecd.org/hpv/ui/Default.aspx).

Akesson, B., Skerfving S. and Mattiasson L. (1988) Experimental study on the metabolism of triethylamine in man. Br. J. Ind. Med. 45: 262-268.

Akesson, B., Vinge E. and Skerfving S. (1989) Pharmacokinetics of triethylamine and triethylamine-N-oxide in man. Toxicol. Appl. Pharmacol. 100: 529-538.

Akesson, B., Skerfving S., Stahlbom B. and Lundh T. (1989) Metabolism of triethylamine in polyurethane foam manufacturing workers. Am. J. Ind. Med. 16: 255-265.

Akesson, B., Floren, I. and Skerfving S. (1985) Visual disturbances after experimental human exposure to triethylamine. Br. J. Ind. Med. 42: 848-850.

Amoore, J.E. and E. Hautala (1983) Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3:272-290.

Ruth, J.H. (1986) Odor thresholds and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47: A142-A151.

Nagata, Y. (2003) Measurement of odor threshold by triangle odor bag method. In: The Ministry of the Environment of Japan (2003): Odor measurement review, Booklet of international workshop on odor measurement, 118-127.

Zeiger E. et al. (1987) Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ. Mutagen. 9: 1-110.

Sorsa M. et al. (1988) Biological and environmental monitoring of occupational exposure to cyclophosphamide in industry and hospitals. Mut. Res. 204: 465-479.

Isakova, GE. Ekshtat, B.Y. and Kerkis Y.Y. (1971) On studies of the mutagenic properties of chemical substances in the establishment of hygenic standards. Hygiene Saint. 36: 178-184.

U.S EPA Integrated Risk Information System: Triethylamine (CASRN 121-44-8) (Last revised at 04/01/1991) (http://www.epa.gov/iris/subst/0520.htm)

Lynch, D.W., Moorman, W.J. Lewis, T.R., Stober, P., Hamlin, R. and Schueler, R.L. (1990) Subchronic inhalation of triethylamine vapor in Fisher-344 rats: Organ system toxicity. Toxicol. Ind. Health. 6: 403-414.

2. Methylisobutylketone

2.1. 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 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.

2.2. 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.

2.3. 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 study, MIBK caused a slight increase in the incidences of renal tubule adenoma and carcinomas in males at the highest dose. The observed increase in chronic progressive nephropathy (CPN) and renal tubular tumors in male rats may have resulted from the well-known male rat specific α2u-globulin accumulation, which is considered to be without relevance to humans. However, since 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) additional yet unknown mechanisms are likely involved (5, 6). 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 relevant to humans and therefore the chronic progressive nephropathy (CPN) in female rats observed at the lowest dose (LOEL = 450 ppm) is used for PDE calculation

or

(ii) relevance of tumor findings at 1800 ppm in male and/or female rats 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

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

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

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

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

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

Rat body weight: 0.425 kg

$$PDE = \frac{225 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 2 \text{ x } 5} = 22.5 \text{ mg/day}$$

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 = 2 severity of effect (CPN in females) with unclear relevance for humans

F5 = 5 because a NOEL for CPN was not established

$$\text{Limit} = \frac{22.5 \text{ x } 1000}{10} = 2250 \text{ ppm}$$

Scenario 2: $NOAEL_{(tumor)}$ 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. Because of lack of evidence of a mouse-specific mode-of-action such as cytotoxic-related regenerative cell proliferation or a receptor-

mediated mechanism the IARC MIBK monograph concludes that the relevance to humans of the liver tumor findings in mice cannot be excluded (6).

A NOEL for carcinogenicity of 900 ppm is used for calculating the oral PDE.

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

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

$$\text{Daily dose} = \frac{0.658\ \text{mg l}^{-1} \text{ x } 43\ \text{l day}^{-1}}{0.028\ \text{kg}} = 1011\ \text{mg/kg/day}$$

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

Mouse body weight: 0.028 kg

$$PDE = \frac{1011 \text{ x } 50}{12 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x } 1} = 42.1\ \text{mg/day}$$

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 = 10 because of severity of endpoint (cancer)

F5 = 1 because a NOEL was established

$$\text{Limit} = \frac{42.1 \text{ x } 1000}{10} = 4210\ \text{ppm}$$

2.4. 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) were observed at 3000 ppm along with 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 NOAEL for reproductive effects was 2000 ppm, the highest concentration tested; the NOAEL for neonatal toxicity was 1000 ppm, based on acute CNS depressive effects (3).

2.5. 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 based upon the LOAEL for chronic progressive nephropathy in female rats from the NTP 2-year inhalation study is 22.6 mg/day. Therefore, it is recommended that MIBK be placed into Class 2 in Table 2 in the ICH Impurities: Residual Solvents Guideline.

2.6. References

Connelly J.C., Hasegawa R., McArdle J.V., Tucker M.L. (1997) ICH Guideline Residual Solvents. Pharmeuropa (Suppl) 9:57.

European Chemicals Bureau; IUCLID Dataset, 4-Methylpentan-2-one (CAS # 108-10-1) p.70 Available from, as of September 24, 2007: http://esis.jrc.ec.europa.eu/

Nemec M.D., Pitt, J.A., Topping, D.C., Gingell, R., Pavkov, K. L., Rauckman E. J. and Harris, S.B. (2004) Inhalation two-generation reproductive toxicity study of methyl isobutyl ketone in rats. Int J Toxicol 23: 127-143.

National Toxicology Program (NTP). Toxicology and Carcinogenesis Studies of Methyl Isobutyl Ketone (CAS No. 108-10-1) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). US Department of Health and Human Services, Public Health Service, National Institutes of Health; Research Triangle Park, NC: 2007. Technical Report Series No. 538.

Stout M.D., Herbert R.A., Kissling G.E. et al. (2008) Toxicity and carcinogenicity of methyl isobutyl ketone in F344N rats and B6C3F1 mice following 2-year inhalation exposure. Toxicology 244: 209–219.

IARC (2012) Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water, IARC Monographs 101: 305-324.