INTERNATIONAL CONFERENCE ON HARMONIZATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS GUIDELINE

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS PDE FOR TRIETHYLAMINE AND PDE OF METHYLISOBUTYLKETONE

Released for Consultation
at *Step 2* of the ICH Process
on 11 June 2015
by the ICH Steering Committee

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the ICH regions (the European Union, Japan, the USA, Health Canada and Switzerland) for internal and external consultation, according to national or regional procedures.

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS
PDE FOR TRIETHYLAMINE (TEA) AND PDE OF METHYLISOBUTYLKETONE (MIBK)

CURRENT *STEP 2* VERSION

Code	History	Date
PDE for TEA and PDE of MIBK	Approval by the Steering Committee under *Step 2* and release for public consultation. • Permitted Daily Exposure (PDE) for Triethylamine (TEA): Addition of PDE based on new toxicological data. • PDE for Methylisobutylketone (MIBK): Revision of PDE based on new toxicological data.	11 June 2015

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS

PDE FOR TRIETHYLAMINE AND PDE OF METHYLISOBUTYLKETONE

Draft ICH Consensus Guideline

Released for Consultation, 11 June 2015, at *Step 2* of the ICH Process

TRIETHYLAMINE

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).

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.

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, 1.4 or 14 mg/kg/day) triethylamine in drinking water was cited in the United States Environemental 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 2 47 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.

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.

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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 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 CPN in female rats observed at the lowest dose (LOEL[1] = 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)

[1] Lowest Observed Effect Level

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

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

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

Rat respiratory volume: 290 L day^{-1}
Rat body weight: 0.425 kg

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

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$_{(\text{tumor})}$ 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 International Agency for Research on Cancer (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

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

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 Central Nervous System (CNS) 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 based upon the Lowest Observed Adverse Effect Level (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.

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