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Step 2b

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ICH HARMONISED GUIDELINE

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS Q3C(R8)

PDE FOR 2-METHYLTETRAHYDROFURAN, CYCLOPENTYL METHYL ETHER, AND TERTIARY-BUTYL ALCOHOL

Draft version

Endorsed on 25 March 2020

Currently under public consultation

Note : This document contains only the PDE levels for three solvents: 2-methyltetrahydrofuran, cyclopentylmethylether and tert-butanol that were agreed to be included in the ICH Q3C(R8) revision. Further to reaching *Step 4*, these PDEs would be integrated into a complete Q3C(R8) Guideline document.

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 Assembly to the regulatory authorities

of the ICH regions for internal and external consultation, according to national or regional procedures.

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS
PDE FOR 2-METHYLTETRAHYDROFURAN (2-MTHF), CYCLOPENTYL METHYL ETHER (CPME), AND TERTIARY BUTYL ALCOHOL (TBA)

Document History

Code	History	Date
Q3C(R8)	Endorsement by the Members of the ICH Assembly under *Step 2* and released for public consultation (document dated 14 February 2020)	25 March 2020

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

2-METHYLTETRAHYDROFURAN

Introduction

2-Methyltetrahydrofuran (2-MTHF, synonyms: 2-Methyloxolane, Tetrahydrosylvan; Tetrahydro-2-methylfuran; CAS Number 96-47-9) is a colourless, volatile liquid with ether-like odour. 2-MTHF is an organic solvent usually synthesized as a racemic mixture consisting of two enantiomeric forms ((S)+ and (R)-). Solubility in water is limited and decreases with increasing temperature. It has a vapour pressure of 136 mbar (20°C) (1).

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

Genotoxicity

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

Carcinogenicity

No data for 2-MTHF are available.

Reproductive toxicity

No reliable information about reproductive toxicity is available. In an acute embryo toxicity and teratogenicity test in zebrafish, 2-MTHF was tested at concentrations ranging from 860 – 8600 mg/L (4). Acute embryo toxicity was observed for 2-MTHF at a nominal LC_{50} value of 2980 mg/L. Sublethal effects were also observed, such as an increase in oedema at nominal concentrations ≥ 1720 mg/L, as well as an increased number of embryos without detectable blood circulation and

insufficient pigmentation at a nominal concentration of 2580 mg/L. Teratogenic effects were not observed with 2-MTHF in this assay.

Repeated-dose toxicity

Two 3-month oral repeated-dose toxicity studies in Crl:CD (SD) rats have been described with 2-MTHF; one without an additional recovery period (2) and one with an additional 1-month recovery period (5). The top dose in the first study was 26 mg/kg/day (2) and in the second study 1000 mg/kg/day (5). 2-MTHF treatment-related observations were not seen in the first study (2). In the second study, groups of 10 male and 10 female rats per dose group were treated with doses of 80, 250, 500 and 1000 mg/kg/day (5). An additional 1-month treatment-free recovery period was added for 5 animals/sex of the control and the high dose groups. Treatment-related observations were generally seen only at doses ≥ 500 mg/kg/day. Besides slight effects on kidney weights (increased at ≥ 500 mg/kg/day), blood cholesterol (increase at 1000 mg/kg/day) and prothrombin time (decreased at ≥ 500 mg/kg/day), the only test article-related microscopic observation was hepatocellular centrilobular hypertrophy at 1000 mg/kg/day. However, no effects were observed in the recovery group and the observed effects can therefore be regarded as completely reversible (5). The NOEL in the second study was considered to be 250 mg/kg/day.

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

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

F1 = 5 to account for extrapolation from rats to humans
F2 = 10 to account for differences between individual humans
F3 = 5 for a 3-month study in rodents
F4 = 1 because no severe effects were observed
F5 = 1 because a NOEL was established

Conclusion

The calculated PDE for 2-MTHF is 50 mg/day based upon the NOEL of the rat sub-chronic oral study. Since the proposed PDE is greater than or equal to 50 mg/day, it is recommended that 2-MTHF be placed into Class 3 “Solvents with low toxic potential” in Table 3 in the ICH Impurities: Residual Solvents Guideline.

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CYCLOPENTYL METHYL ETHER

Introduction

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

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

CPME is classified as an irritant to skin (H315) and eye (H319) in accordance with EC No 1272/2008, in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). CPME did not show the potential to induce skin sensitization in the Local Lymph Node Assay. In rats, LD_{50} for acute oral exposure is 1000–2000 mg/kg, for dermal exposure it is greater than 2000 mg/kg, and for inhalation exposure it is greater than 21.5 mg/L. No human toxicity data have been reported (2).

Genotoxicity

The results of genotoxicity tests have been reported (1,2). CPME was not mutagenic genotoxic in the AMES bacterial reverse mutation assays in *S. typhimurium* test strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2 *uvrA* with and without metabolic activation at concentrations up to 5710 µg/plate (1) and 5000 µg/plate (2). Negative results were also obtained in *in vitro* mammalian chromosome aberration tests in human lymphocytes at concentrations up to 1.1 mg/mL and in Chinese Hamster Lung cells at concentrations up to 1.0 mg/mL (2). An *in vivo* rat micronucleus test integrated in a 3-month oral repeated-dose study up to a dose of 31 mg/kg/day (1) and an *in vivo* mammalian erythrocyte micronucleus test in CD-1 mice at single oral doses up to 2000 mg/kg/ (2) also did not indicate any genotoxic potential. In conclusion, there is no evidence that CPME is genotoxic.

Carcinogenicity

No data are available.

Reproductive toxicity

In a two-generation reproductive toxicity study, CPME was administered to rats in drinking water at doses of 313, 1250 or 5000 mg/mL (5). Other than decreased body weights of pups in the F1 generation and F2 generation which were observed at the highest dose, no other significant changes

in reproductive parameters were reported. The NOAEL of this study was estimated to be 193.45 mg/kg/day (1250 mg/L in drinking water). However, as detailed toxicity information from this study is not available, this study was not used to support the calculation of a PDE.

Repeated-dose toxicity

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

In a 28-day study with a 14-day recovery period, Crj: Crl:CD(SD) rats were administered CPME by oral gavage at 15, 150 or 700 mg/kg/day in corn oil (2,6). Six unscheduled deaths occurred in males at 700 mg/kg/day between days 12 and 15 of treatment and were attributed to poor clinical conditions. Salivation was commonly observed in males and females at 700 mg/kg/day. Salivation occurred twice in one male at 150 mg/kg/day however this finding was not considered adverse. Decreased motor activity, piloerection, abnormal gait, tremors, convulsion, hunched posture, fast respiration, and thin appearance were observed in males at 700 mg/kg/day. Decreased body weight gain was observed in females at 700 mg/kg/day. All clinical findings and changes in bodyweight gains resolved after the recovery period. There were no other toxicological effects of CPME in this study. The NOEL of this study was determined to be 150 mg/kg/day.

In a 90-day study, Sprague Dawley Crl:CD(SD) rats were administered up to 31 mg/kg/day CPME by oral gavage in corn oil (1). There were no CPME-related ante-mortem or post-mortem findings. Detailed information on the experimental design and study results such as clinical signs, haematology and blood chemistry findings were not publicly available, although the authors considered the NOEL of this study to be 31 mg/kg/day.

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

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

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

F1 = 5 to account for extrapolation from rats to humans

F2 = 10 to account for differences between individual humans

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

F4 = 1 because no severe effects were observed

F5 = 1 because a NOEL was established

Conclusion

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

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TERTIARY-BUTYL ALCOHOL

Introduction

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

The rat oral LD_{50} (lethal dose for 50% of animals, combined values for males and females) has been reported to be between 2733 and 3500 mg/kg body weight. The primary acute effects observed in animals are signs of alcoholic intoxication. Human clinical test data indicate that TBA is neither an irritant nor a sensitizer (3). Its potency for intoxication is approximately 1.5 times that of ethanol (4). Given its wide diversity of use, the potential for human exposure to TBA is high (5). The National Institute for Occupational Safety and Health (NIOSH) indicates its use is widespread in the workplace (1). A Cosmetic Ingredient Review Expert Panel also concluded that TBA is safe as used in cosmetic products (3).

Genotoxicity

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

Carcinogenicity

TBA was investigated by the US National Toxicology Program (NTP) in two drinking water studies, one in F344/N rats and one in B6C3F1 mice (1,6). Both studies included three treatment groups (60 animals/sex/group; 50 animals/sex/group completed the study): in rats, doses of 85, 195, and 420 mg/kg/day in males and 175, 330, and 650 mg/kg/day in females; in mice, doses of 535, 1035, and 2065 mg/kg/day in males and 510, 1015, and 2105 mg/kg/day in females) (1). Survival was decreased in high dose rats and high dose male mice. Final mean body weights were decreased in exposed male and high dose female rats and high dose female mice. The primary

targets of TBA were the kidney (mineralization, hyperplasia, tumours) in male rats and the thyroid gland (follicular cell hyperplasia, tumours) and urinary bladder (inflammation and epithelial hyperplasia) in mice. The NTP Technical Report concluded that there was some evidence of carcinogenic activity in male rats based on increased incidences of renal tubule adenoma or carcinoma (combined) and in female mice based on increased incidences of follicular cell adenoma of the thyroid gland (6). There was no evidence of carcinogenicity in female rats and equivocal evidence in male mice.

In mice, the incidence of thyroid follicular cell adenoma was significantly increased in high dose females. These tumorigenic effects were associated with an increased incidence and severity of focal follicular cell hyperplasia of the thyroid gland in all TBA-treated groups of males and females (1,6). In contrast, no thyroid tumours were observed in an 18-month carcinogenicity study of methyl *tert*-butyl ether (MTBE) by the inhalation route in CD-1 mice (7). The systemic TBA exposure (as a metabolite of MTBE) likely exceeded the exposure in the NTP study (2). However, differences in strain of mice (CD-1 versus B6C3F1) or route of administration may be responsible for the differences in response. In the absence of evidence suggesting direct thyroid toxicity, it was hypothesized that TBA induced thyroid tumours in the drinking water study through increased liver metabolism of thyroid hormones, triggering a compensatory increase in thyroid stimulating hormone (TSH) production and, thus, thyroid follicular cell proliferation and hyperplasia (2). Rodents are substantially more sensitive than humans to the development of thyroid follicular cell tumours in response to thyroid hormone imbalance. Thus, the dose response is non-linear and tumours are not expected to occur in humans in the absence of altered thyroid hormone homeostasis (8,9). In partial agreement with the above hypothesis, TBA is an inducer of Phase I and II liver enzymes following 14 days of oral exposure at doses less than or equal to those used in chronic studies and TBA administration resulted in a small decrease in circulating thyroid hormones in B6C3F1 mice (10). However, no meaningful changes in TSH levels were observed in this study. A comprehensive review of the mouse carcinogenicity data concluded that, in the absence of meaningful effect on TSH and toxicity to the thyroid, the cause of the increase in either hyperplasia or adenoma incidence remains unclear (2). TBA administration also resulted in an increased incidence of chronic inflammation and hyperplasia of the transitional epithelium of the urinary bladder in high-dose males and females.

In rats, an increased incidence of renal tubule adenomas and carcinomas was observed in males exposed to TBA, but the increase was not dose-dependent. The evidence suggests that these tumours are due to a α2μ-globulin nephropathy-mediated mode of action. α2μ-Globulin

nephropathy is a well-recognized sex- and species-specific mechanism of toxicity without relevance to humans (11,12). Foci of linear mineralization in the renal medulla, a lesion consistently reported as a long-term consequence of α2μ-globulin nephropathy, were observed in the high dose male rats (1,6). Further, TBA was shown to interact with α2μ, which explains the accumulation of α2μ in the male rat kidney (5). Although no significant neoplastic findings were observed in female rats, a dose-dependent increase in severity of nephropathy was observed at all TBA doses compared to control animals (average severity of 1.6, 1.9, 2.3, and 2.9; scale of 0–4); incidence ranged from 47–48 out of 50 animals in all groups. An increased incidence of transitional epithelial hyperplasia and suppurative inflammation at the two highest doses and renal tubule hyperplasia in a single high dose animal were also observed. The human relevance of the renal findings in female rats is currently unclear.

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

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

or

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

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

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

F1 = 5 to account for extrapolation from rats to humans

F2 = 10 to account for differences between individual humans

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

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

F5 = 5 because a NOEL for nephropathy was not established

Limit = (35 x 1000)/10 = 3500 ppm

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

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

F1 = 12 to account for extrapolation from mice to humans
F2 = 10 to account for differences between individual humans
F3 = 1 because long duration of treatment (2 years)
F4 = 1 because hyperplasia response was of minimal to mild average severity at all doses and thyroid tumours were not observed at the low dose
F5 = 5 because a NOEL for hyperplasia was not established

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

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

Reproductive toxicity

TBA has not been associated with induction of skeletal or visceral malformations in rats or mice but did induce developmental delays and intrauterine or prenatal mortality at doses of 1000 mg/kg/day or greater (2).

In a reproduction/developmental toxicity screening study, TBA was administered to Sprague-Dawley rats (12/sex/group) by oral gavage at dose levels of 0, 64, 160, 400, and 1000 mg/kg/day for up to 63 days in males and from 4 weeks prior to mating until postnatal day (PND) 20 in females (13). There were no adverse effects on any reproductive parameters including mating index, fertility index, pregnancy index, or gestation index. For dams receiving 1000 mg/kg/day TBA through gestation and lactation, there was a significant reduction in mean litter size, a decrease in the number of live born per pregnancy, an increase in the number of stillborn pups, increased pup mortality up to PND 4, and a decrease in mean pup body weight at birth, which continued to

weaning. Parental toxicity (transient CNS effects, reduced body weight and food consumption) was observed at doses of 400 mg/kg or greater. The NOAEL for developmental/reproductive effects was identified as 400 mg/kg/day.

At a dose of 1000 mg/kg/day, mild to moderate transient systemic toxicity was observed in both sexes in the parental generation including reversible central nervous system (CNS) effects such as lethargy and ataxia, and reduced food consumption and weight gain. At 400 mg/kg/day, an increased incidence of transient mild lethargy/ataxia in females was observed. The NOEL for parental toxicity was 160 mg/kg/day.

Repeated-dose toxicity

In a sub-chronic toxicity study, TBA was administered to F344/N rats (10/sex/dose) *ad libitum* in drinking water at dose levels of 0, 2.5, 5, 10, 20 and 40 mg/mL for 13 weeks (equivalent to 176, 353, 706, 1412 and 2824 mg/kg/day) (6). All high dose males and six high dose females died during the study. Nephropathy was the most sensitive effect observed in the study. An increase in severity of nephropathy was observed in the lower four dose groups in males when compared to control animals as was the accumulation of hyaline droplets in the kidney at doses of 353, 706, and 1412 mg/kg/day. The incidence of nephropathy in females at the highest three doses was significantly greater than that of the controls. Transitional epithelial hyperplasia and inflammation of the urinary bladder were observed at the two highest doses in males and in high dose females. Based on the nephropathy in male rats at the lowest dose, 176 mg/kg/day was considered the LOEL. As noted above, α2μ-globulin nephropathy is a well-recognized sex and species-specific mechanism of toxicity without relevance to humans (11,12).

TBA was also administered to B6C3F1 mice (10/sex/dose) in the drinking water for 13 weeks at the same concentrations provided to rats (doses equivalent to 446, 893, 1786, 3571 and 7143 mg/kg/day) (6). Two high dose males and one high dose female died. The final mean body weights in males at the two highest doses and in females at the high dose were significantly lower than that of the control animals. Transitional epithelial hyperplasia and inflammation were observed in the urinary bladder of the same groups. A NOEL of 1786 mg/kg/day was identified (6).

Conclusion

The calculated PDE for TBA is 35 mg/day based upon the LOEL for nephropathy in females from the 2-year rat carcinogenicity study. It is recommended that TBA be placed into Class 2 "Solvents to be limited" in Table 2 in the ICH Impurities: Residual Solvents Guideline.

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