



# ICH Q3C(R8) Impurities: Guideline for Residual Solvents

**Step 4 document – to be implemented**

**22 April 2021**

International Council for Harmonisation of Technical Requirements  
for Pharmaceuticals for Human Use

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## Background

- **The ICH Q3C core Guideline reached *Step 4* in 1997.**
- **The document was originally developed based on a Concept Paper (10 March 1994)**
- **A maintenance agreement was instituted in 1999 and a Maintenance Expert Working Group (EWG) was formed.**
- **The agreement provided for the re-visitation of solvent Permitted Daily Exposure (PDE) and allowed for minor changes to the guideline that included the existing PDEs.**
- **It was also agreed that new solvents and PDEs could be added based upon adequate toxicity data.**

## **Key Principles**

- **ICH Q3C provides Permissible Daily Exposures (PDEs) for residual solvents**
- **PDEs are defined as pharmaceutically acceptable intakes of residual solvents**
- **Residual solvents are classified based on the evaluation of their possible risk to human health**
  - Class 1 solvents: Solvents to be avoided
  - Class 2 solvents: Solvents to be limited
  - Class 3 solvents: Solvents with low toxic potential

## Guideline Objectives

- **The current revision (R8) provides PDEs for three new residual solvents:**
  - 2-Methyltetrahydrofuran
  - Cyclopentyl Methyl Ether
  - Tertiary Butyl Alcohol

## Table of Contents

- **2-Methyltetrahydrofuran (2-MTHF)**
  - Toxicological data
  - Identified PDE
- **Cyclopentyl Methyl Ether (CPME)**
  - Toxicological data
  - Identified PDE
- **Tertiary Butyl Alcohol (TBA)**
  - Toxicological data
  - Identified PDE

## Summary of Guideline Content

- **This revision to the Q3C Guideline provides PDEs for 3 new residual solvents as follows:**
  - 2-Methyltetrahydrofuran: 50 mg/day
  - Cyclopentyl Methyl Ether: 15 mg/day
  - Tertiary Butyl Alcohol: 35 mg/day

## 2-MTHF

- EWG's review of available toxicity data with 2-MTHF
  - Genotoxicity: no evidence for genotoxicity
  - Carcinogenicity: no data available
  - Reproductive toxicity: no evidence for reproductive toxicity
  - Repeat dose toxicity: two rat sub-chronic oral studies; No-observed-effect-level (NOEL) considered appropriate for PDE calculation

## 2-MTHF: PDE calculation\*

\*see Q3C guideline for details of PDE calculation

- Rat sub-chronic (3-month) oral studies
  - Effects at 500 mg/kg/day or greater included changes in kidney weight, cholesterol, prothrombin time, and hepatocellular hypertrophy
  - NOEL of 250 mg/kg/day used for PDE
  - PDE = 50 mg/day
- Since the PDE is greater than or equal to 50 mg/day, 2-MTHF is placed into Class 3 (“solvents with low toxic potential”)

## CPME

- EWG's review of available toxicity data with CPME
  - Genotoxicity: no evidence for genotoxicity
  - Carcinogenicity: no data available
  - Reproductive toxicity: a 2-generation study in rats demonstrated decreased body weights of pups; however, detailed information from study is not available.
  - Repeat dose toxicity: two rat sub-chronic oral studies and one rat sub-chronic inhalation study; No-observed-effect-level (NOEL) from rat 28-day oral study considered most appropriate for PDE calculation.

## CPME: PDE calculation\*

\*see Q3C guideline for details of PDE calculation

- Rat sub-chronic (28-day) oral study
  - Effects at 700 mg/kg/day (high dose) included lethality, salivation, increased respiration, and CNS effects.
  - NOEL of 150 mg/kg/day (mid dose) used for PDE
  - PDE = 15 mg/day
- Since CPME is associated with significant toxicities and a PDE of 15 mg/day, CPME is placed into Class 2 (“solvents to be limited”)

## TBA (1)

- EWG's review of available toxicity data with TBA
  - Genotoxicity: no evidence for genotoxicity
  - Reproductive toxicity: limited data available.
    - Some evidence of induced developmental delays and mortality at relatively high oral doses.
    - Additional reports of reduced mean litter size, number of live born pups and pup body weight, and increased pup mortality and number of stillborn pups.

## TBA (2)

- EWG's review of available toxicity data with TBA
  - Repeat dose toxicity: two sub-chronic oral (drinking water) studies in rats and mice
    - In rats:
      - Lethality observed at highest dose (2824 mg/kg/day)
      - Other key findings included nephropathy and hyperplasia/inflammation of the urinary bladder.
      - Lowest-observed-effect-level (LOEL) of 176 mg/kg/day identified due to increased incidence of nephropathy.
    - In mice:
      - Lethality observed at highest dose (7143 mg/kg/day)
      - Other key findings included reduced body weight and hyperplasia/inflammation of the urinary bladder at the two highest doses
      - NOEL of 1786 mg/kg/day was identified.

## TBA (3)

- EWG's review of available toxicity data with TBA
  - Carcinogenicity:
    - TBA was studied in 2-year rat and mouse drinking water studies
    - Primary targets of TBA toxicity and carcinogenicity were the kidney in rats, and thyroid gland and urinary bladder in mice
    - NTP's conclusion: "some evidence of carcinogenic activity" in male rats and female mice
  - The 2-year carcinogenicity studies were considered the most appropriate to support calculation of the PDE
    - Individual PDEs were calculated for each study (see following slides)

## TBA: PDE calculation\*

\*see Q3C guideline for details of PDE calculation

- Rat 2-year study:
  - Renal lesions and tumour findings in male rats are not relevant to humans
  - Increased severity in nephropathy observed in female rats at all doses used for PDE calculation (LOEL = 175 mg/kg/day)
  - PDE = 35 mg/day
- Since TBA is associated with significant toxicities and a PDE of 35 mg/day, TBA is placed into Class 2 (“solvents to be limited”)

## Results of Public Consultation

- **All comments received during the public consultation period were considered and revisions made when warranted.**
- **Revisions of note were made to the evaluation of 2-Methyltetrahydrofuran and included additional background information and a summary of a reproductive toxicity study in rats that did not impact the PDE calculation.**
- **The recommended PDEs remain unchanged from the Step 2 document.**

## Conclusions

- **A Q3C Maintenance procedure evaluated 3 new solvents: 2-MTHF, CPME, and TBA**
- **The identified PDEs are as follows:**
  - 2-MTHF: 50 mg/day (Class 3)
  - CPME: 15 mg/day (Class 2)
  - TBA: 35 mg/day (Class 2)

## Contact

- **For any questions please contact the ICH Secretariat:**

**[admin@ich.org](mailto:admin@ich.org)**