# Q3C(R8) Impurities: Guidance for Residual Solvents

Guidance for Industry

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**December 2021**
**ICH**

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# FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

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**PART VI:**

*Contains Nonbinding Recommendations*

# Q3C(R8) Impurities: Guidance for Residual Solvents
# Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

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

This guidance provides recommendations for permitted daily exposures (PDEs) for three additional residual solvents: (1) 2-methyltetrahydrofuran, (2) cyclopentyl methyl ether, and (3) tert-butyl alcohol. This guidance is intended to recommend acceptable amounts for these residual solvents in pharmaceuticals for the safety of the patient. As part of the maintenance process for the ICH guidance for industry *Q3C Impurities: Residual Solvents* (December 1997),[2] the Q3C PDE levels are added and revised as new toxicological data for solvents become available.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

[1] This guidance was developed within the Expert Working Group (Quality) of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Assembly at *Step 4* of the ICH process, April 2021. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the ICH regions.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

## 2-METHYLTETRAHYDROFURAN

### Introduction

2-Methyltetrahydrofuran (2-MTHF, synonyms: 2-methyloxolane, tetrahydrosylvan; tetrahydro-2- methylfuran; CAS Number 96-47-9) is a colorless, volatile liquid with ether-like odor. 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 vapor pressure of 102 millimeters of mercury (mmHg) (20°C) (1). For practical reasons, 2-MTHF is a racemic mixture when used as a solvent in synthetic processes.

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

### Genotoxicity

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

### Carcinogenicity

No data for 2-MTHF are available.

### Reproductive and developmental toxicity

2-MTHF was tested in a good laboratory practice-compliant prenatal developmental toxicity study according to Organization for Economic Co-operation and Development (OECD) TG414 in rats with doses of 100, 300, and 1,000 milligrams per kilogram per day (mg/kg/day) (Ref. 4). At 1,000 mg/kg/day, 2-MTHF caused slightly reduced maternal weight gain, slightly lower gravid uterus weight, and marginally reduced fetal body weight. Only slight effects on fetal growth were observed, and overall fetal survival and development were considered unaffected at the highest dose. The no-observed-adverse-effect level (NOAEL) was considered 1,000 mg/kg/day. However, because detailed toxicity information is not available, this study was not used to support the calculation of a PDE. In an acute embryo toxicity and teratogenicity test in zebrafish, 2-MTHF was tested at concentrations ranging from 860 – 8,600 milligrams/liter (mg/L) (Ref. 5). Acute embryo toxicity was observed for 2-MTHF at a nominal lethal concentration 50% (LC50) value of 2,980 mg/L. Sublethal effects were also observed, such as an increase in edema at nominal concentrations ≥ 1,720 mg/L, as well as an increased number of embryos without detectable blood circulation and insufficient pigmentation at a nominal concentration of 2,580 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 racemate — one without a recovery period (Ref. 2) and one with a 1-month recovery period (Ref. 6). The top dose in the first study was 26 mg/kg/day (Ref. 2), and in the second study 1,000 mg/kg/day (Ref. 6). 2-MTHF treatment-related observations were not seen in the first study (Ref. 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 1,000 mg/kg/day (Ref. 6). The 1-month treatment-free recovery period included five animals/sex for the control and the high-dose groups. Treatment-related observations were generally seen at doses ≥ 500 mg/kg/day. Besides slight effects on kidney weights (increased at ≥ 500 mg/kg/day), blood cholesterol (increased at 1,000 mg/kg/day), and prothrombin time (decreased at ≥ 500 mg/kg/day), the only test article-related microscopic observation was hepatocellular centrilobular hypertrophy at 1,000 mg/kg/day. However, no effects were observed in the recovery group and the observed effects can therefore be regarded as completely reversible. The no-observed-effect level (NOEL) in the second study was considered 250 mg/kg/day.

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

$$PDE = \frac{25 \times 50}{\frac{0}{5 \times 10 \times 5 \times 1 \times 1}} = 50 \text{ mg/day}$$

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

Limit = (50 x 1,000)/10 = 5,000 ppm

**Conclusion**

The calculated PDE for 2-MTHF is 50 milligrams per day (mg/day) based upon the NOEL of the rat sub-chronic oral study. Since the PDE is 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 Q3C guidance.

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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 (Refs. 1 and 2).

The vapor pressure of CPME is 44.9 mmHg at 25°C, the Log Pow is 1.59, and the water solubility is 1.1 grams per 100 grams (23 °C) (Refs. 3 and 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. CPME did not show the potential to induce skin sensitization in the local lymph node assay. In rats, LD50 (lethal dose for 50 percent of animals) for acute oral exposure is 1,000–2,000 milligrams/kilogram (mg/kg), for dermal exposure it is greater than 2,000 mg/kg, and for inhalation exposure it is greater than 21.5 mg/L. No human toxicity data have been reported (Ref. 2).

### Genotoxicity

The results of genotoxicity tests have been reported (Refs. 1 and 2). CPME was not mutagenic 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 5,710 micrograms per plate (Ref. 1) and 5,000 micrograms per plate (Ref. 2). Negative results were also obtained in in vitro mammalian chromosome aberration tests in human lymphocytes at concentrations up to 1.1 milligrams per milliliter (mg/mL) and in Chinese hamster lung cells at concentrations up to 1.0 mg/mL (Ref. 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 (Ref. 1) and an in vivo mammalian erythrocyte micronucleus test in CD-1 mice at single oral doses up to 2,000 mg/kg (Ref. 2) also did not indicate any genotoxic potential. In conclusion, there is no evidence that CPME is genotoxic.

### Carcinogenicity

No data are available.

### Reproductive and developmental toxicity

In a two-generation reproductive toxicity study, CPME was administered to rats in drinking water at doses of 313, 1,250, or 5,000 mg/mL (Ref. 5). Other than decreased body weights of pups in the F1 generation and F2 generation that 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 (1,250 mg/L in drinking water). However, because 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 (Refs. 2 and 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 (Ref. 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, hematology, and blood chemistry findings, were not publicly available, although the authors considered the NOEL of this study to be 31 mg/kg/day. In another 90-day study, Sprague Dawley rats were administered up to 500 mg/kg/day CPME by oral gavage in water (Ref. 7). The NOAEL of this study was estimated to be 32 mg/kg/day. However, because detailed toxicity information from this study is not publicly available and this study was not conducted under Good Laboratory Practice, this study was not used to support the calculation of a PDE.

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 hours/day, 5 days/week) by whole-body inhalation exposure (Ref. 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.

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

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

Limit = (15 x 1,000)/10 = 1,500 ppm

**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 Q3C guidance.

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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 is used for a variety of purposes, including as an alcohol denaturant, a dehydration agent, and a solvent (Ref. 1). TBA is soluble in water and has a vapor pressure of 31 mmHg (20°C). TBA is rapidly absorbed following inhalation or ingestion, but poorly absorbed through skin (Ref. 2).

The rat oral LD50 (combined values for males and females) has been reported to be between 2,733 and 3,500 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 (Ref. 3). Its potency for intoxication is approximately 1.5 times that of ethanol (Ref. 4). Given its wide diversity of use, the potential for human exposure to TBA is high (Ref. 5). The National Institute for Occupational Safety and Health indicates that TBA's use is widespread in the workplace (Ref. 1). A Cosmetic Ingredient Review Expert Panel also concluded that TBA is safe as used in cosmetic products with concentrations ranging from 0.00001 to 0.3 percent (Ref. 3).

### Genotoxicity

TBA was not mutagenic in the Ames bacterial reverse mutation assay (Ref. 6). The U.S. 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 40,000 parts per million (ppm) TBA in drinking water for 13 weeks or up to 625 mg/kg administered by intraperitoneal injection 3 times at 24-hour intervals (Ref. 6). In conclusion, there is no evidence that TBA is genotoxic (Ref. 2).

### Carcinogenicity

TBA was investigated by the NTP in two 2-year drinking water studies, one in F344/N rats and one in B6C3F1 mice (Refs. 1 and 6). Both studies included 3 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; and in mice, doses of 535, 1,035, and 2,065 mg/kg/day in males, and 510, 1,015, and 2,105 mg/kg/day in females) (Ref. 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, tumors) in male rats, and the thyroid gland (follicular cell hyperplasia, tumors) 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 (Ref. 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 (Refs. 1 and 6). In contrast, no thyroid tumors were observed in an 18-month carcinogenicity study of methyl *tert*-butyl ether by the inhalation route in CD-1 mice (Ref. 7). The systemic TBA exposure (as a metabolite of methyl *tert*-butyl ether) likely exceeded the exposure in the NTP study (Ref. 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 tumors in the drinking water study through increased liver metabolism of thyroid hormones, triggering a compensatory increase in thyroid stimulating hormone production and, thus, thyroid follicular cell proliferation and hyperplasia (Ref. 2). Rodents are substantially more sensitive than humans to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance. Thus, the dose response is nonlinear, and tumors are not expected to occur in humans in the absence of altered thyroid hormone homeostasis (Refs. 8 and 9). In partial agreement with the above hypothesis, TBA is an inducer of phase 1 and 2 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 (Ref. 10). However, no meaningful changes in thyroid stimulating hormone levels were observed in this study. A comprehensive review of the mouse carcinogenicity data concluded that, in the absence of meaningful effect on thyroid stimulating hormone and toxicity to the thyroid, the cause of the increase in either hyperplasia or adenoma incidence remains unclear (Ref. 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 tumors are due to an 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 (Refs. 11 and 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 (Refs. 1 and 6). Further, TBA was shown to interact with α2μ, which explains the accumulation of α2μ in the male rat kidney (Ref. 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 tumor findings in male rats are not relevant to humans and, therefore, the increased severity in nephropathy observed in female rats at the lowest dose (lowest-observed- effect level (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 1,000)/10 = 3,500 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 tumors were not observed at the low dose

F5 = 5 because a NOEL for hyperplasia was not established

Limit = (42.5 x 1000)/10 = 4,250 ppm

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

**Reproductive and developmental 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 1,000 mg/kg/day or greater (Ref. 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 1,000 mg/kg/day for up to 63 days in males and from 4 weeks before mating until postnatal day 20 in females (Ref. 13). There were no adverse effects on any reproductive parameters, including mating index, fertility index, pregnancy index, or gestation index. For dams receiving 1,000 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 pups per pregnancy; an increase in the number of stillborn pups; increased pup mortality up to postnatal day 4; and a decrease in mean pup body weight at birth, which continued to weaning. Parental toxicity (transient central nervous system 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 1,000 mg/kg/day, mild to moderate transient systemic toxicity was observed in both sexes in the parental generation, including reversible central nervous system 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, 1,412, and 2,824 mg/kg/day) (Ref. 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 1,412 mg/kg/day. The incidence of nephropathy in females at the highest three doses was significantly greater than that in 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 (Refs. 11 and 12).

TBA was also administered to B6C3F1 mice (10/sex/dose) in drinking water for 13 weeks at the same concentrations provided to rats (doses equivalent to 446, 893, 1,786, 3,571, and 7,143 mg/kg/day) (Ref. 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 in the control animals. Transitional epithelial hyperplasia and inflammation were observed in the urinary bladder of the same groups. A NOEL of 1,786 mg/kg/day was identified (Ref. 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 Q3C guidance.

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