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

DRAFT CONSENSUS GUIDELINE

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS PDE FOR CUMENE

Released for Consultation
at *Step 2* of the ICH Process

on 26 March 2010

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 three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

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PDE FOR CUMENE

CURRENT *STEP 2* VERSION

Code	History	Date
PDE for Cumene	Approval by the Steering Committee under *Step 2* and release for public consultation. Once the revision reaches *Step 4*, it will be incorporated as part IV in the core document currently named Q3C(R4), which will then be renamed Q3C(R5).	26 March 2010

IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS

PDE FOR CUMENE

Draft ICH Consensus Guideline

Released for Consultation, 26 March 2010, at *Step 2* of the ICH Process

Introduction

Cumene [synonyms: Cumol; isopropylbenzene; isopropylbenzol; (1-methyl/ethyl)benzene; 2-phenylpropane] is listed in the ICH Q3C guideline in Class 3, i.e. as a solvent with low toxicity. A summary of the toxicity data used by the EWG to establish a Permitted Daily Exposure (PDE) value for cumene at the time when the ICH Q3C guideline was signed off at *Step 2* in November 1996 is published in Connelly et al. (1).

According to this report from the EWG no data from carcinogenicity studies with cumene were available. Regarding genotoxicity data cumene was reported negative in an Ames test and in *Saccaromyces cerevisiae* and positive in *in vitro* UDS and cell transformation assays using mouse embryo cells. Calculation of a PDE value was based on a rat toxicity study published in 1956. Female Wistar rats were given cumene at doses of 154, 462 and 769 mg/kg by gavage 5 days/week for 6 months. No histopathological changes but slight increases in kidney weights at the two higher doses were observed suggesting a NOEL of 154 mg/kg. It was concluded that the PDE for cumene is 55.0 mg/day i.e., cumene is a solvent with low toxicity to be listed in Class 3. (1)

Meanwhile new toxicity data have been published including results from NTP 2-year inhalation studies showing that cumene is carcinogenic in rodents. (2) A reappraisal of the PDE value of cumene according to the maintenance agreement from 1999 is therefore initiated. For establishing a revised PDE value in this document the standard approaches (modifying factors, concentration conversion from ppm to mg/L, values for physiological factors) as described in detail in Connelly et al. (1) were used.

Genotoxicity

Cumene was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535, when tested with and without liver S9 activation enzymes. Cumene induced small, but significant, increases in micronucleated polychromatic erythrocytes in bone marrow of male rats treated by intraperitoneal injection. In contrast, no increase in micronucleated erythrocytes was observed in peripheral blood of male (up to 1000 ppm) or female (up to 500 ppm) mice exposed to cumene by inhalation for 3 months. (2)

p53 and K-*ras* mutations were found in 52% and 87% of lung neoplasms in exposed mice compared to 0% and 14% in the chamber controls, respectively. This pattern of mutations identified in the lung tumors suggests that DNA damage and genomic instability may be contributing factors to the development of lung cancer in mice. (3) However, the overall genotoxic profile does not provide sufficient evidence for a direct mutagenic mode of action of cumene or its metabolites as the primary cause in tumorigenesis. (2)

Carcinogenicity

F344 rats were exposed to concentrations of 250, 500, or 1000 ppm of cumene in air by inhalation 6h/day, 5 days/week for 2 years. Increased incidences of respiratory epithelial adenoma in the nose and renal tubule adenoma or carcinoma (combined) in males at all dose levels. Increased incidences of respiratory epithelium adenoma in the nose in females at all dose levels. (2)

Molecular weight of cumene: 120.19

LOEL 250 ppm (a NOEL for carcinogenic effects was not established)

$$250\ \text{ppm} = \frac{250 \text{ x } 120.19}{24.45} = 1229\ \text{mg/m}^3 = 1.23\ \text{mg/l}$$

$$\text{For continuous dosing} = \frac{1.23 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.22\ \text{mg/l}$$

$$\text{Daily dose} = \frac{0.22\ \text{mg l}^{-1} \text{ x } 290\ \text{l day}^{-1}}{0.425\ \text{kg}} = 150\ \text{mg/kg/day}$$

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

$$PDE = \frac{150 \text{ x } 50}{5 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x } 10} = 1.50\ \text{mg/day}$$

F1 = 5 to account for extrapolation from rats to humans
F2 = 10 to account for differences between individual humans
F3 = 1 because long duration of treatment (105 weeks)
F4 = 10 because oncogenic effect was reported
F5 = 10 because a NOEL was not established

$$\text{Limit} = \frac{1.5 \text{ x } 1000}{10} = 150\ \text{ppm}$$

B6C3F1 mice were exposed to concentrations of 125, 250, or 500 ppm (females) or 250, 500, or 1000 ppm (males) of cumene in air by inhalation 6h/day, 5 days/week for 2 years. Increased incidences of alveolar/bronchiolar neoplasms in males and females at all dose levels. Incidences of hepatocellular adenoma or carcinoma (combined) showed a dose-related increase in female mice. (2)

LOEL 125 ppm (female mice)

$$125\ \text{ppm} = \frac{125 \text{ x } 120.19}{24.45} = 614\ \text{mg/m}^3 = 0.61\ \text{mg/l}$$

$$\text{For continuous dosing} = \frac{0.61 \text{ x } 6 \text{ x } 5}{24 \text{ x } 7} = 0.11 \text{ mg/l}$$

$$\text{Daily dose} = \frac{0.11 \text{ mg l}^{-1} \text{ x } 43 \text{ l day}^{-1}}{0.028 \text{ kg}} = 169 \text{ mg/kg/day}$$

Mouse respiratory volume: 43 l day^{-1}
Mouse body weight: 0.028 kg

$$PDE = \frac{169 \text{ x } 50}{12 \text{ x } 10 \text{ x } 1 \text{ x } 10 \text{ x } 10} = 0.70 \text{ mg/day}$$

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 (105 weeks)
F4 = 10 because oncogenic effect was reported
F5 = 10 because a NOEL was not established

$$\text{Limit} = \frac{0.7 \text{ x } 1000}{10} = 70 \text{ ppm}$$

Conclusion

The main carcinogenic effects in the rodent studies can be related to the inhalation route of administration (respiratory and olfactory tissues) and may therefore not be relevant for a residual solvent in (mainly) orally applied pharmaceuticals. However, systemic carcinogenic effects were also reported (kidney in male rats, liver in female mice) and the use of the NTP study data for calculation of a PDE is therefore considered appropriate.

The former PDE for this solvent was greater than 50 mg/day (55 mg/day) and cumene was placed in Class 3. The newly calculated PDE for cumene based upon carcinogenicity data is 0.7 mg/day, therefore, **it is recommended that cumene be placed into Class 2** in Table 2 in the ICH Impurities: Residual Solvents Guideline.

References

1. Connelly JC, Hasegawa R, McArdle JV, Tucker ML. ICH Guideline Residual Solvents. Pharmeuropa (Suppl) 1997;9:57.
2. Toxicology and Carcinogenesis Studies of Cumene (CAS No. 98-82-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Natl Toxicol Program Tech Rep Ser 2009;542;NIH 09-5885.
3. Hong HHL, Ton TVT, Kim Y, Wakamatsu N, Clayton NP, Chan PC et al. Genetic Alterations in K-*ras* and *p53* Cancer Genes in Lung Neoplasms from B6C3F1 Mice Exposed to Cumene. Toxicol Pathol 2008;36:720-726.