



Q3C(R6) Impurities: Guideline for Residual Solvents

PDE for Triethylamine and Methylisobutylketone

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ICH Q3C(R6)

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Outline

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 - Proposed PDE
- Methylisobutylketone
 - Toxicological data
 - Proposed PDE
- Conclusions

Background –Q3C Maintenance

- ICH Q3C core guidance reached *Step 5* in 1997.
- In 1999 a maintenance agreement was instituted 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 guidance that included the **existing PDEs**.
- It was also agreed that **new solvents** and PDEs could be **added** based upon adequate toxicity data.

Objectives of current maintenance process

A Maintenance process has been proposed in 2014

1. To add a **new solvent** to the guideline, **Triethylamine**
2. To **revise** the existing **PDE** of the solvent **Methylisobutylketone**, as new toxicological data for this solvent become available

Triethylamine (TEA)

- EWG's review of available toxicity data with TEA:
 - Genotoxicity: limited data, no evidence for genotoxicity
 - Carcinogenicity: no data available
 - Reproductive toxicity: no robust studies for PDE calculation
 - Repeated dose toxicity: rat sub-chronic inhalation study; No-observed-effect-level (NOEL) considered appropriate for PDE calculation;
 - Due to study deficiencies other published animal toxicity data were disregarded from determining a PDE

TEA: PDE calculation*

*see Q3C guideline for details of PDE calculation

- Rat sub-chronic (28 weeks) inhalation study
 - No treatment related effects at all dose groups
 - NOEL of 247 ppm (highest dose) used for PDE
 - PDE = 62.5 mg/day
- Since the PDE is greater than 50mg/day TEA is placed into Class 3 (“solvents with low toxic potential“)

Methylisobutylketone (MIBK)

- MIBK is listed in the Q3C core guideline of 1997 in Class 3 (= solvent with low toxic potential)
- Review of toxicity data available at that time resulted in a PDE of 100 mg/day
- Due to new data from US National Toxicology Program (NTP) 2-year rodent carcinogenicity studies the existing PDE has been revisited

MIBK: New NTP data

- MIBK has been studied by NTP in 2-year rat and mouse inhalation studies
- Primary targets of MIBK toxicity and carcinogenicity were the kidney in rats and the liver in mice
- NTP's conclusion: "some evidence" of carcinogenic activity in rats and mice
- The International Agency for Research on Cancer IARC classified MIBK as a group 2B carcinogen ("possibly carcinogenic to humans")

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MIBK: PDE calculation*

*see Q3C guideline for details of PDE calculation

- Rat carcinogenicity data: two different scenarios for PDE calculation
 1. Tumor findings not relevant to humans (rat specific mode of action); PDE calculated for chronic progressive nephropathy in females (Lowest-observed-effect-level LOEL = 450 ppm);
PDE = 45 mg/day
 2. Relevance of tumor findings to humans cannot be excluded; NOEL of 900 ppm is used for PDE calculation;
PDE = 45 mg/day

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MIBK: PDE calculation*

*see Q3C guideline for details of PDE calculation

- In mouse study MIBK increased incidence of hepatocellular adenoma/carcinoma in females and males at highest dose (1800 ppm)
 - There is clear evidence of a constitutive androstane receptor (CAR)-mediated mode of action (MOA) for the mouse liver tumors.
 - This MOA is not relevant for humans; therefore no PDE calculation was done based on mouse tumor data.

New PDE value for MIBK

- The former PDE of MIBK was 100 mg/kg and the solvent was placed in Class 3.
- The newly calculated PDE is based upon the NOEL for tumors in male and female rats and the LOEL for chronic progressive nephropathy in female rats from 2-year inhalation study.
- In both cases a PDE of 45 mg/day was calculated.
- Therefore, MIBK is placed into Class 2.

Conclusion (1)

- A Q3C Maintenance process has been initiated to add a new solvent TEA and revise the PDE of MIBK.
- The proposed PDE for TEA is 62.5 mg/day; TEA is placed into Class 3.
- The proposed PDE for MIBK is 45 mg/day; MIBK is placed into Class 2.
- Both PDE values have been adopted by the Assembly under Step 4 on November 9, 2016.

Conclusion (2)

- The PDE for TEA and MIBK document has been integrated as part V in the core Q3C(R5) Guideline which was then renamed Q3C(R6).
- The Table 2, Table 3 and Appendix 1 have been updated to reflect the revision of the PDE for TEA and MIBK.



Thank You!

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