



Final Concept Paper

Q3C(R5): Impurities : Guideline for Residual Solvents

(Revision of the ICH Q3C(R4) Guideline to account for new toxicity data related to cumene)

14 May 2009

Endorsed by the Steering Committee on 10 June 2009

Type of Harmonisation Action Proposed

Maintenance of ICH Q3C.

Statement of the Perceived Problem

The ICH Q3C guidance reached *Step 5* in December of 1997. It had been agreed by the members of the Expert Working Group (EWG) that the permissible daily exposure (PDE) could be modified if reliable and more relevant toxicity data was brought to the attention of the group. In 1999, a maintenance agreement was instituted and a Maintenance EWG was formed. The agreement provided for the re-visitation of solvent PDEs 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.

Solvents with Low Toxic Potential - Solvents in Class 3 (*shown in Table 3*) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5% under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice.

Issues to be Resolved

Cumene, synonyms: Cumol; isopropylbenzene; isopropylbenzol; (1-methyl/ethyl)benzene; 2-phenylpropane is listed in Class 3 solvents with low toxicity. New toxicity data occurs for cumene. Male and female F344/N rats and B6C3F1 mice were exposed to cumene (greater than 99.9% pure) by inhalation for 2 weeks, 3 months, or 2 years.

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity* of cumene in male F344/N rats based on increased incidences of respiratory epithelial adenoma in the nose and renal tubule adenoma or carcinoma (combined). There was *some evidence of carcinogenic activity* of cumene in female F344/N rats based on the incidences of respiratory epithelium adenoma in the nose. There was *clear evidence of*

carcinogenic activity of cumene in male B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms. There was *clear evidence of carcinogenic activity* of cumene in female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms. Increased incidences of hepatocellular adenoma or carcinoma (combined) in female mice were also considered to be related to exposure to cumene. In addition genetic alterations in *K-ras* and *p53* cancer genes in lung neoplasms from B6C3F1 mice exposed to cumene were detected.

Background to the Proposal

1. U. S. National Toxicology Program (NTP).TR-542 <http://ntp.niehs.nih.gov/go/29250>;
2. Hong 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.

Type of Expert Working Group

The Q3C EWG will be comprised of two members (one chemist and one toxicologist) nominated by the six sponsors of the ICH and one member nominated by IGPA, WSMI and by each pharmacopeia.