Toxicity

In this guide

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6. CIT is acutely nephrotoxic in mice and rats, rabbits, pigs and poultry, causing swelling and eventual necrosis of the kidneys. CIT also affects liver function but to a lesser extent. Both in vitro and in vivo studies have provided clear evidence for reproductive and developmental toxicity of CIT (EFSA, 2012).

Previous assessments

EFSA 2012 opinion

7. In 2012, the European Food Standards Agency (EFSA) assessed the risks to public and animal health related to the presence of CIT in food and feed.

Toxicokinetic

8. The available information on CIT shows it is eliminated predominantly by renal excretion; approximately 75 % of radiolabelled citrinin (14C-citrinin) given by intraperitoneal dose was recovered in urine (Reddy et al., 1982). Toxicokinetic studies with oral administration of CIT were not available.

Toxicity

9. The acute lethal toxicity of CIT ranged from 19-134 mg/kg bw depending on species and route of administration (EFSA, 2012). The main changes in pathology were degeneration and necrosis of the kidneys in all species indicating nephrotoxicity. Repeat dosing studies confirmed the nephrotoxicity of CIT and highlighted the differences in susceptibility between species. Necropsy showed histopathological changes in the kidneys of all species tested (except hamsters), which were consistent with the acute signs observed.

Genotoxicity and Carcinogenicity

10. EFSA concluded that the available data indicated that CIT is not mutagenic in conventional bacterial assays either with or without metabolic activation by S9 fraction (EFSA, 2012). Mutagenicity in the Ames test was only reported in one study when rat hepatocytes were used as the activating system (Sabater-Vilar et al., 1999). In mammalian cells in vitro, CIT did not induce DNA single-strand breaks, oxidative DNA damage or sister chromatid exchanges (SCE) but induced micronuclei, aneuploidy and chromosomal aberrations.

11. In vivo CIT induced chromosome abnormalities and hypodiploidy in the bone marrow of mice exposed at concentrations of 5-20 mg/kg bw for eight weeks, by oral administration (Jeswal, 1996).

12. An 80-week feeding study exposed rats to CIT in the diet at initially about 70 mg/kg bw per day, the kidney was identified as the main target organ with reported incidences of adenomas (Arai and Hibino, 1983). EFSA concluded that given the observed high incidence of adenomas it cannot be excluded that carcinomas would have occurred if the exposure time had been increased to the full length of a carcinogenicity study (at least two years).

Immunotoxicity

13. EFSA concluded that the data on immunotoxicity of CIT were incomplete and often non-specific and therefore did not allow for a conclusive evaluation.

Developmental and reproductive toxicity

14. Data from in vitro and in vivo studies reported reproductive toxicity and teratogenic and embryotoxic effects of CIT (EFSA, 2012). However, in vivo studies also reported maternal toxicity, including nephrotoxicity, indicating that the reproductive, teratogenic and embryotoxic effects of CIT may be secondary to

maternal toxicity.

15. Kinetic investigations in pregnant rats provided no conclusive data about the percentage of CIT that crosses the placenta (Reddy et al., 1982b). EFSA could not determine the extent to which the offspring were exposed based on the available data.