Health based guidance values

In this guide

European Food Safety Authority

38. In 2012, EFSA concluded that the establishment of a HBGV for citrinin would not be appropriate, given the available data on genotoxicity and the limitations and uncertainties in the database.

39. For compounds that are potentially genotoxic or carcinogenic, EFSA normally recommends the use of the MOE approach. However, EFSA did not consider an MOE approach appropriate for citrinin due to the lack of human dietary exposure data. Instead, EFSA decided to characterise the risk of citrinin and determine a level of no concern for nephrotoxicity in humans. A level of no concern is not a HBGV but is a concentration below which there is no appreciable concern for nephrotoxic effects. This level does not specifically address other end points.

40. The level of no concern was based on a no observed adverse effect level (NOAEL) of 20 µg/kg bw per day determined from a study in rats by Lee and Pan (2010) (detailed in paragraph 21). EFSA applied a default uncertainty factor (UF) of 100 for interspecies (10) and interindividual (10) variation to derive a level

of no concern of 0.2 µg/kg bw per day for nephrotoxicity.

41. EFSA however noted that a concern for genotoxicity and carcinogenicity could not be excluded at the level of no concern for nephrotoxicity.

National Institute for Public Health and Environment (RIVM)

42. In 2015, the NVWA commissioned the RIVM to produce a report based on a literature search to determine whether toxicity studies published since the EFSA opinion could be used to derive a BMD or a HBGV.

43. From the studies retrieved, the RIVM selected the developmental toxicity study by Singh et al. (2014) (paragraph 32) and the subchronic toxicity study by Hayashi et al. (2012) (paragraph 30) for BMD analysis.

44. The lowest BMDL derived was the BMDL05 of 48 µg/kg bw/day for ‘decreased crown rump length’ from the Singh et al. (2014) study; the study was considered the appropriate POD for risk assessment. The RIVM noted that effects on the foetuses could be secondary to maternal toxicity. Since information on maternal effects was limited (only maternal body weight was measured), effects on foetuses were considered relevant and the BMDL05 on decreased crown rump length the most appropriate. This BMDL05 was 2.4 times higher than the NOAEL determined by EFSA in 2012.

45. The RIVM concluded that there were no new scientific articles available in the years 2011 to 2015 on the *in vivo* genotoxicity or carcinogenicity of citrinin. A re-evaluation of the study by Arai and Hibino (1983) (detailed in paragraph 17) on the tumorigenicity of citrinin in rats revealed that the study was not suitable for BMD analysis. Therefore, the RIVM agreed with EFSA’s conclusion regarding the genotoxicity and/or carcinogenicity of citrinin and did not derive a HBGV. The RIVM further supported EFSA’s request for a well-designed toxicological study in laboratory animals to further explore the carcinogenic potential of citrinin.

The Committee on Toxicity of Chemicals in Food, Consumer products and the Environment

46. Based on the assessment by EFSA in 2012 and new data published between 2012-2024 the COT agreed that citrinin is nephrotoxic. In addition, and of specific interest to the assessment on maternal toxicity, both *in vitro* and *in vivo* studies indicate that dietary exposure to citrinin may cause reproductive and developmental toxicity, although most of the effects occur at maternally toxic doses.

47. Overall, the new data published since the 2012 EFSA opinion supported previous findings or added to the existing knowledge base regarding citrinin.

48. The COT therefore agrees with EFSA that a HBGV cannot currently be set and that it is appropriate to use the level of no concern for nephrotoxicity to characterise the risk of citrinin to consumers. Whilst the RIVM BMDL05 specifically covers reproductive effects, it is 2.4 times higher than EFSA’s level of no concern for nephrotoxicity. Therefore, the level of no concern for nephrotoxicity is adequately protective for maternal, reproductive and developmental toxic effects.