Health based guidance values

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European Food Safety Authority

38. In 2012, EFSA concluded that the establishment of a HBGV 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 recommends the use of the margin of exposure (MOE) approach. However, for CIT, EFSA did not consider an MOE approach appropriate due to the lack of human dietary exposure data. Instead, EFSA decided to characterise the risk of CIT 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 et al. (2010) (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 ug/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 benchmark dose (BMD) or a HBGV.

43. From the studies retrieved, the RIVM selected two for BMD analysis, the study by Singh et al. (2014) (paragraph 32), a developmental toxicity study, and the study by Hayashi et al. (2012) (paragraph 30), a 70- and 90- day toxicity study.

44. The lowest BMDL derived was 48 µg/kg bw/day for ‘decreased crown rump length’ from the Singh et al. (2014) study; the study was considered the appropriate point of departure (POD) for risk assessment. This BMDL is 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 (1983) (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 COT

46. Based on the assessment by EFSA in 2012 and new data published between 2012-2024 the COT agreed that CIT is acutely nephrotoxic. Of specific interest to the assessment on maternal toxicity, both *in vitro* and *in vivo* studies

have provided some evidence that dietary exposure to citrinin may cause reproductive and developmental toxicity, although most of the effects observed were at maternally toxic doses.

47. Overall, the new data published since the 2012 EFSA opinion supported previous findings or added to the overall knowledge base of CIT.

48. The COT therefore agreed with EFSA that a HBGV cannot be set and that it was appropriate to use a level of no concern for nephrotoxicity to characterise the risk of CIT to consumers. Whilst the RIVM BMDL specifically covers reproductive effects, it is 2.4 times the level of no concern by EFSA. Therefore, the level of no concern for nephrotoxicity would be adequately protective for maternal, reproductive and developmental toxic effects.