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

Statement on the potential risk from citrinin in the maternal diet: Lay summary

1. The Scientific Advisory Committee on Nutrition (SACN) is reviewing the evidence that relates to the Government's dietary recommendations for women of childbearing age. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from certain chemicals in the maternal diet. The following statement sets out the advice of the COT on whether estimated UK exposures to citrinin would pose a risk to maternal health, that is, adversely affect maternal outcomes during pregnancy, childbirth and up to 24 months after delivery.

2. Citrinin is a toxic substance produced by several species of fungi. It occurs mainly in grains but is also found in other products of plant origin including beans, fruits, fruit and vegetable juices, herbs and spices as well as in spoiled dairy products. Its occurrence is generally due to the growth of fungi during the storage of crops after harvest.

3. In 2014, the Food Standards Agency (FSA) carried out a survey, the Total Diet Study, to estimate the background exposure of UK consumers to various chemicals, including citrinin, from the whole diet and to determine trends in exposure. Animal-derived foods were included in the Total Diet Study, but citrinin was not detected in any of the animal-derived food products

analysed and therefore, the carryover of citrinin from animal feed into animal-based foods is not considered in this assessment.

4. Citrinin has also been reported as a contaminant in certain fermentation products such as red yeast rice (RYR). However, the majority of the packaging of RYR supplements either states that the product is not suitable for children and/or women who are pregnant or breast feeding or recommends that these groups should consult a general practitioner prior to consumption; therefore, RYR supplements have not been considered in this assessment.

5. Experimental studies in animals have linked citrinin to kidney and liver toxicity. In the kidney, the main adverse effects following citrinin administration were degeneration and tissue death, which were observed in all species tested. In the liver, a significant decrease in liver weight as a fraction of body weight (relative liver weight or liver to body weight ratio) has been reported.

6. Data from in vitro (cell) and animal studies also suggest that citrinin may be associated with reproductive toxicity, including adverse effects on the developing foetus during pregnancy. However, in experimental studies, these effects usually occur at doses that cause harm, including kidney damage, to the pregnant female. This suggests that any effects on the developing offspring are secondary to maternal toxicity. Animal studies also suggest that citrinin can cross the placenta, although there is limited evidence to support this.

7. No epidemiological or human case report studies specific to the UK population were available. However, studies from non-UK countries (Belgium, Czech Republic, Portugal, Germany, Haiti, Bangladesh, Nigeria, Turkey, and Tunisia) that monitored citrinin levels in human urine did not indicate an association between higher maternal daily intakes of citrinin and duration of pregnancy, birth weight, birth length or head circumference at birth.

8. In 2012, the European Food Safety Authority (EFSA) assessed the risks to public and animal health related to the presence of citrinin in food and animal feed.

9. EFSA noted that citrinin does not seem to cause mutations in bacteria but that citrinin can induce chromosome changes in mammalian cells and in mice. These changes can be associated with the development of cancer. Citrinin has been shown to cause kidney tumours in rats; however, EFSA could not predict whether citrinin might cause cancer in humans because of a lack of lifetime exposure studies in animals.

11. The evidence concerning potential DNA damage and the lack of human dietary exposure data led EFSA to conclude that establishing either a safety limit or following a margin of exposure approach for citrinin would not be appropriate. Instead, EFSA used the evidence from a study in rats to identify a “level of no concern” of 0.2 µg per kg body weight per day for kidney toxicity in humans. A level of no concern is not a safety limit; rather, it is a level of exposure below which there is no significant concern that adverse effects could occur.

12. In 2015, the Netherlands Food and Consumer Product Safety Authority (NVWA) commissioned the National Institute for Public Health and Environment (RIVM) to find out whether any new studies on the toxic effects of citrinin had been published since 2011.

13. The RIVM selected two studies in rodents to identify the lowest dose of citrinin that is linked to a 5% increase in adverse effects (the Benchmark Dose Lower Confidence Limit, $BMDL_{05}$). The value they calculated was 48 µg per kg body weight per day for foetal growth restriction measured as decreased crown rump length, the length of a foetus from the top of the head to the rump (bottom), excluding the legs. This was 240 times higher than the dose set by EFSA as the level of no concern for kidney toxicity, suggesting that exposures below the level of no concern are very unlikely to cause adverse effects on foetal development and further supporting the idea that any effects on the developing offspring are likely to be secondary to maternal toxicity.

14. The COT agreed with EFSA's level of no concern of 0.2 µg per kg body weight per day for kidney toxicity and the way in which it had been established. They noted that whilst the $BMDL_{05}$ derived by the RIVM was specific to reproductive effects, since EFSA's level of no concern was 240 times lower, complying with it would therefore provide protection against all the other forms of toxicity reported, including maternal and reproductive toxic effects, as well as adverse effects to the developing foetus during pregnancy.

15. Estimated exposures of women of childbearing age to citrinin were below the level of no concern set by EFSA. Therefore, the estimated exposures were not of concern for kidney or reproductive toxicity or for adverse effects to the developing foetus during pregnancy. In addition, citrinin was not detected above the lowest level that can be reliably measured in any of the food groups considered, further confirming that dietary exposure to citrinin is low and supporting the conclusion that levels of citrinin in the diet are not of concern to UK consumers.

16. Due to limitations in the database, the COT concluded that the risk of DNA damage or cancer cannot be ruled out. The COT agreed with EFSA and the RIVM that there is a need for further research to identify whether citrinin can damage DNA and/or increase the risk of cancer.