This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

TOX/2024/39

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

Discussion paper on the potential risk from citrinin in the maternal diet

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health, in its reports on 'The influence of maternal, foetal and child nutrition on the development of chronic disease in later life' (SACN, 2011) and on 'Feeding in the first year of life' (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.

2. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments e.g., in the area of food safety advice. This subject was initially discussed during the Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) horizon scanning item at their January 2020 meeting with a scoping paper being presented to the COT in July 2020. This included background information on a provisional list of chemicals proposed by SACN. It was noted that the provisional list of chemicals was subject to change following discussion by COT who would be guiding the toxicological risk

assessment process: candidate chemicals or chemical classes can be added or removed as the COT considered appropriate. The list was brought back to the COT with additional information in September 2020. Following a discussion at the September 2020, COT agreed that papers on a number of compounds should be prioritised. The following paper provides the advice of the COT on whether exposure to citrinin would pose a risk to maternal health.

Background

3. Unless otherwise indicated, the following background information has been taken from the European Food Standards Agency's (EFSA) scientific opinion on the risks for public and animal health related to the presence of citrinin in food and feed (2012).

4. Citrinin (CIT) is a mycotoxin produced by several species of fungi of the genera *Aspergillus*, *Penicillium* and *Monascus* and is generally formed after harvest under storage conditions. It occurs mainly in grains but can also occur in other products of plant origin e.g. beans, fruits, fruit and vegetable juices, herbs and spices as well as in spoiled dairy products. In addition, CIT is found as an undesirable contaminant in red mould rice (RMR) which is used as a food preservative and colourant in Asian foods and as a supplement.

5. Experimental data indicate that CIT residues may occur in edible tissues and eggs following oral exposure of animals with highly contaminated feed materials.

Transfer of CIT from feed to meat and animal products

6. EFSA identified one study on the potential carry over of CIT from animal feeds into edible tissues and eggs (Abdelhamid and Dorra, 1990). Laying hens received feed with a CIT concentration of 100 µg/kg for 6 weeks. CIT residues of 10.4 ± 2.1 µg/kg egg yolk, 6.16 ± 1.2 µg/kg egg white, 10.3 ± 1.75 µg/kg

white muscles and 9.84 ± 1.45 µg/kg red muscles were measured (Abdelhamid and Dorra, 1990). No CIT residues were detected after a withdrawal period of 2 weeks. EFSA concluded that CIT residues may occur in edible tissues and eggs following oral exposure of animals with contaminated feed materials.

7. A more recent study by Meerpoel et al. (2020a), not included in the EFSA opinion) looked at the carry-over of CIT into animal products following the administration of CIT. For 3 weeks, pigs (n = 16) were exposed to feed containing 1 mg CIT/kg feed or to control feed (n = 4), while 2 groups of broiler chickens and laying hens (n = 8 per group) received 0.1 mg CIT/kg feed and 3 or 3.5 mg CIT/kg feed, respectively, or control feed (n = 4). CIT concentrations were quantified in plasma, kidneys, liver, muscle and eggs. CIT was detected in all collected tissues, except for muscle and egg white in hens in the lowest dose group, and egg white in hens in the highest dose group. CIT concentrations in plasma ranged from 0.1 ng/mL (laying hens in lower dose group) - 20.8 ng/mL (pigs). In tissues, CIT concentrations ranged from 0.6 (muscle) - 20.3 µg/kg (liver) in pigs, while concentrations in chickens ranged from 0.1 (muscle) - 70.2 µg/kg (liver). Carry-over ratios from feed to edible tissues were calculated by the authors as 0.1 to 2% in pigs, and between 0.1 and 6.9% in chickens, suggesting a low contribution of pig and poultry tissue-derived products towards the total dietary CIT intake for humans.

8. The carryover of CIT from feed into animal products has not been included in the exposure assessment.

Red Yeast Rice

9. CIT is an undesirable contaminant in *Monascus* fermentation products such as red yeast rice (RYR) also known as red mould rice (RMR), used in Asian cuisine as a food colorant and flavour enhancer. RYR contains

monacolins, with monacolin K being structurally identical to lovastatin, a drug which lowers cholesterol. Hence, RYR is also used as a dietary supplement claiming to decrease plasma triglyceride and cholesterol levels (Wei et al., 2003).

10. In 2019, the maximum level (ML) for CIT in RYR preparation was reduced from 2000 µg/kg to 100 µg/kg in Commission Regulation (EC) No 1881/2006 (amendment: Commission Regulation (EU) 2019/1901). FSA Policy colleagues have confirmed that while red yeast *Monascus purpureus* is traditionally used in China as a food colouring, it is not authorised as food colour/additive under Regulation 1333/2008, including for supplements.

11. In 2017, EFSA reported that of the 92 samples of RYR food supplements tested (obtained in the EU), 37 samples (40%) were positive for CIT and three samples exceeded the EU ML at the time of 2,000 µg/kg (EFSA, 2017). Based on the EFSA exposures it has been calculated here that 10 of the 92 samples tested would exceed the amended ML of 100 µg/kg.

12. The majority of packaging for RYR supplements states that the product is either a) not suitable for children and/or women who are pregnant or breast feeding, or b) it is recommended these groups should consult a general practitioner (GP) prior to consumption. Due to the warnings on the packaging, RYR supplements have not been considered further in this assessment.

Toxicity

13. 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.

Summary of EFSA 2012 opinion

14. In 2012, EFSA assessed the risks to public and animal health related to the presence of CIT in food and feed and concluded that the derivation of a health-based guidance value (HBGV) would not be appropriate, given the available data on genotoxicity and the limitations and uncertainties in the current database.

15. 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 of 0.2 µg/kg bw per day. This was based on a no observed effect level (NOAEL) of 20 µg/kg bw per day determined from the 90 day study by Lee et al. (2010) in rats (see paragraph 25). A default uncertainty factor (UF) of 100 was applied, 10 for interspecies and 10 for interindividual variation.

16. EFSA concluded that a concern for genotoxicity and carcinogenicity cannot be excluded at the level of no concern for nephrotoxicity.

Toxicokinetic

17. The available information on CIT shows it is eliminated predominantly by renal excretion, approximately 75 % of radiolabelled citrinin (^{14}C-citrinin) given by intraperitoneal dose was recovered in urine (Reddy et al., 1982).

18. ^{14}C-CIT was administered to pregnant female rats by subcutaneous injection of a dose of 35 mg/kg bw on the 12th day of gestation. Elimination of ^{14}C-CIT-derived radioactivity from plasma was found to be biphasic. The half-lives for the rapid (alpha) and slower (beta) phases of elimination were 1.95 hours and 39.7 hours, respectively. Approximately 74 % of the radioactivity appeared in the urine in the first 24 hours, with only 1.7 % and 1.4 % in the urine at 48 hours and 72 hours, respectively.

19. Toxicokinetic studies with oral administration of CIT were not available.

Acute toxicity

20. The acute lethal toxicity of CIT ranged from 19-134 mg/kg bw depending on species and route of administration.

21. The median lethal dose (LD_{50}) for oral administration (105-134 mg/kg bw in mouse and rabbit) was higher than intravenous, intraperitoneal and subcutaneous administration. Intravenous administration was only documented in rabbit, but this resulted in the lowest LD_{50} (19 mg/kg bw). LD_{50} for subcutaneous and intraperitoneal administration was comparable for rat, mouse, guinea pig and rabbit (35-89 mg/kg bw).

22. The main changes in pathology were degeneration and necrosis of the kidneys in all species indicating nephrotoxicity.

Repeat dose and (sub)chronic toxicity

23. 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 nephrotoxicity seen in the acute studies. Dogs were the most sensitive with intraperitoneal administration of 10 mg/kg bw/day for two weeks leading to spontaneous mortality after 7-11 days. Hamsters tolerated an estimated 50 mg/kg bw/day in feed for two weeks with no clinical signs of toxicity, no gross lesions at necropsy and no histopathological changes.

24. Intraperitoneal administration of 50 mg CIT/kg bw for 2-4 days in guinea pigs led to mortality of all animals and histopathological changes were seen in the kidneys of the deceased guinea pigs (Carlton, 1978). An LD50 value of 43 mg/kg bw was determined in guinea pigs by Thacker et al. (1977) following the oral administration of CIT for 14 days.

25. A 90-day study with male Wistar rats by Lee et al. (2010), aimed to establish a safe concentration for dietary RMR as a food additive. CIT was given in the form of fermented RMR and contained different concentrations of CIT (1, 2, 10, 20 and 200 mg/kg). At the highest dose tested, no toxicologically significant alterations were observed, and the authors concluded that RMR containing CIT at a level of 200 mg CIT/kg RMR (equivalent to 20 µg CIT/kg bw per day) was not nephrotoxic. The authors therefore derived a NOAEL of 20 mg/kg bw per day in rats.

26. An 80-week feeding study exposed rats to CIT in the diet at about 70 mg/kg bw per day initially, however EFSA stated that as the body weight in the treated rats declined throughout the experiment, the estimation of the actual dose was difficult (Arai and Hibino, 1983). The study identified the kidney as the main target organ for toxicity and reported progressive histopathological changes and incidences of adenomas. EFSA concluded that given the observed high incidence of adenomas it cannot be excluded that carcinomas would have occurred if exposure time had been increased to the full length of a carcinogenicity study (at least 2 years).

Genotoxicity

27. Overall, EFSA concluded that the available literature data indicate that CIT is not mutagenic in conventional bacterial assays either with or without metabolic activation by S9 fraction from rat or human liver or rat kidney. Mutagenicity in the Ames test was only reported in one study when rat hepatocytes were used as activating system. In mammalian cells *in vitro*, CIT did not induce DNA single-strand breaks, oxidative DNA damage or sister chromatid exchanges (SCE) but induced micronuclei (MN), aneuploidy and chromosomal aberrations.

28. *In vivo* studies in mice exposed to CIT at concentrations of 5-20 mg/kg bw for eight weeks by oral administration showed the induction of

chromosome abnormalities and hypodiploidy in bone marrow (Jeswal, 1996, abstract only available).

Immunotoxicity

29. EFSA concluded that the data on immunotoxicity of CIT were incomplete and often non-specific, and therefore did not allow for a conclusive evaluation. EFSA further noted that the available studies were old and, in most cases, did not focus on immunology. A study carried out in beagles (20 and 40 mg/kg bw for 2 days administered in gelatine capsules and after that intraperitoneal because of profound emetic effects) report inconsistent changes in leukocyte counts (Carlton et al., 1974). EFSA considered that the results in this study were most likely related to dehydration of CIT treated animals than to any direct effect of CIT (20 and 40 mg/kg bw for 2 days administered in gelatine capsules and after that intraperitoneal because of profound emetic effects).

Developmental and reproductive toxicity

30. Data from *in vitro* and *in vivo* studies reported reproductive toxicity and teratogenic and embryotoxic effects of CIT. However, the *in vivo* studies also reported maternal toxicity, including nephrotoxicity, indicating that the reproductive, teratogenic and embryotoxic effects may be secondary to maternal toxicity. One study in male mice showed adverse effects on male reproductive organs and sperm quality when CIT was given intraperitoneally (0.0625, 0.625 or 6.25 mg/kg bw daily).

31. In mice which received an intraperitoneal dose of 10, 20, 30 or 40 mg CIT/kg bw on one of days 7-10 of gestation, there were no detectable adverse prenatal effects except at dose levels toxic to the dams. (Hood et al., 1976). At doses of 30 and 40mg/kg adverse effects on foetal growth and survival were observed.

32. A single subcutaneous dose of 35 mg citrinin/kg bw on days 3-15 of gestation was administered to rats. No skeletal malformations of the foetuses were observed (Reddy et al., 1982a). However, enlarged kidneys, internal hydrocephalus and cleft palates were reported. While 30-50 % of the pregnant dams died, the resorption rate of foetuses in the treated group was higher than in the controls. The authors concluded that citrinin was an embryocidal and fetotoxic agent, but that maternal toxicity potentially influenced the outcome of this study.

33. Kinetic investigations in pregnant rats provided no conclusive data about the percentage of CIT that crosses the placenta (Reddy et al., 1982b).

34. However, enlarged kidneys, internal hydrocephalus and cleft palates were reported. While 30-50 % of the pregnant dams died, the resorption rate of foetuses in the treated group was higher than in the controls. The authors concluded that CIT was an embryocidal and fetotoxic agent, but that maternal toxicity potentially influenced the outcome of this study.

35. In a series of experiments, the effect of CIT on pregnant Wistar rats and their offspring was investigated. CIT was administered at a concentration of 10 mg/kg feed (equivalent to approximately 1 mg/kg bw) during the gestation period (6 - 20 days post coitum). The dams showed mild maternal toxicity in the liver, intestines and kidneys. Maternal weight gain and feed intake were also reduced (Singh et al., 2007a, 2007b). In the same study, foetal resorption rate was increased and 6.8 % of the examined foetuses showed severe malformations, including internal hydrocephalus and notched and contracted kidneys. About 10 % of all foetuses were retarded with incomplete ossification of the skull bones. Histological investigations of the foetal kidneys showed tubular degeneration, medullar tubular necrosis and interstitial fibrosation (Singh et al., 2008).

36. EFSA concluded that the study performed by Singh et al. confirmed that CIT induces teratogenicity in rodent species. EFSA however noted that

the doses at which effects were seen also induced maternal toxicity and that the extent of offspring exposure could not be determined in this study. Moreover, data on the actual exposure remain inconsistent, as all dams showed reduced feed intake at variable levels. Hence, the deviation from the targeted dose (1 mg/kg bw) was considerable and contributed to the uncertainty of this study.

37. The embryotoxic potential of CIT was also investigated in the chick embryo model (at 1-10 µg, injected subgerminally or intra-amniotically at different days of the egg incubation period) (Vesela et al., 1983). Effects on early embryonic development were observed including embryonic death (up to 60 %), and morphological alteration on embryos heads (exencephaly, micro-ophthalmia and cleft beak).

38. More recent *in vitro* studies with mouse embryonic cells confirmed the previous *in vivo* data. Blastocysts treated with CIT showed apoptosis and significant decreased implantation rates (Chan and Shiao, 2007). An increased rate of apoptosis was observed in mouse embryoblasts following *ex vivo* treatment with CIT at a concentration of 30 µg/mL (Chan, 2007). In further *in vitro* experiments, Chan (2008) observed a significant reduction in the rate of oocyte maturation, fertilization and embryonic development.

39. Qingqing et al. (2012) investigated the effects of CIT on the reproductive organs of male mice. Adult male mice (4 months of age) received an intraperitoneal injection of CIT (0.0625, 0.625 or 6.25 mg/kg bw), daily for 7 days. CIT significantly increased the relative reproductive organ weights and decreased sperm count at all doses. Histopathological changes in the testes were also seen. A significantly lower pregnancy rate was observed when females were mated with the previously exposed males and no embryos occurred in the females mated with males given the highest dose of 6.25 mg/kg bw.

Publications since the EFSA 2012 opinion

40. A literature search was undertaken between 2012 and 2024 to gather any data published following the EFSA opinion on CIT in 2012. The following sections summarise the information found.

Toxicokinetic

41. A study by Degen et al. (2018) exposed two healthy female volunteers to doses of CIT (0.045-0.114 µg/kg) below the NOAEL for nephrotoxicity set by EFSA (2012), on two occasions, several weeks apart. CIT was dissolved in ethanol and added to a soft drink. Urinary excretion showed that ingested CIT undergoes conversion to dihydrocitrinone (DH-CIT) which is then excreted in the urine along with the remaining parent compound. The cumulative urinary excretion within 24 hours was between 32.9% and 70.8% of the sum of CIT and DH-CIT. The median half-life in urine was 6.7 hours for CIT and 8.9 hours for DH-CIT.

42. Meerpoel et al. (2020b) carried out toxicokinetic analysis of CIT in pigs and broiler chickens. CIT (50 µg/kg bw for pigs, 250 µg/kg bw for chickens) was administered to four animals of each species by oral gavage or intravenous injection. The author states that that oral bioavailability for CIT was complete for broiler chickens (113–131%) and 37-44% in pigs with CIT more rapidly absorbed in pigs (T_{max} = 0.92 hours) compared to broiler chickens (T_{max} = 7.33 hours). Elimination of CIT was slower in pigs ($T_{1/2el}$ = 26.81 hours after intravenous administration) compared to chickens ($T_{1/2el}$ = 1.97 hours after intravenous administration) with the clearance rate higher in broiler chickens (C_{liv}=9.87 mL/h/kg for pigs versus C_{liv} = 863.09 mL/h/kg for broilers). The results also showed that the volume of distribution differed significantly between pigs (V_d = 0.30 L/kg after intravenous administration) and chickens (V_d = 2.46 L/kg after intravenous administration).

In vitro

43. Chinese hamster lung fibroblast cells were treated with concentrations of either CIT (0.1–100 µM CIT) or DH-CIT (0.1–300 µM) (Föllmann et al.,

2014). The cytotoxic potency of DH-CIT (IC_{50} of 320/200 µM) after treatment for 24 and 48 hours was lower compared with CIT (IC_{50} of 70/62 µM). The authors concluded that the lower cytotoxicity of DH-CIT indicated it was a detoxification step.

44. The interaction between DH-CIT and albumin did not show significant species differences when tested with human, bovine, porcine, and rat albumins (Faisal et al., 2019). The presence of albumin however significantly decreased the acute *in vitro* cytotoxic effects of both DH-CIT and CIT on a MDCK cell line.

Genotoxicity

45. Föllmann et al. (2014) carried out an *in vitro* micronucleus (MN) assay on V79 cells (Chinese hamster lung fibroblasts) with 10–100 µM CIT and 1–500 µM DH-CIT. The results indicated that CIT induced a concentration-dependent increase in MN frequencies at concentrations ≥ 30 µM, while its metabolite DH-CIT showed no genotoxic effect up to 300 µM.

46. Anninou et al. (2014) investigated the genotoxicity of CIT on a Hep3B cell line at concentrations below those detected in human serum (10^{-12}–10^{-6} M). Results showed enhanced sister chromatid exchanges (SCEs) at low (pM) concentrations, but not in a dose dependent manner.

47. A study by Tsai et al. (2023; abstract only), exposing human renal proximal tubule epithelial cells (hRPTECs) to CIT (10 and 20 µM) over 3 days showed chromosomal aberrations. Exposure of human embryonic kidney 293 (HEK293) cells to CIT at the same concentration for 3 and 30 days significantly promoted mitotic spindle abnormalities, wound healing, cell migration, and anchorage-independent growth. The authors concluded that both short- and long-term CIT exposure activated cancer and cell cycle-related signalling pathways.

Acute toxicity

Reproductive and developmental toxicity

48. Newly fertilised zebrafish eggs were exposed to concentrations of 50, 25, 12.5, 6.25, 3.125, 1.56, and 0.78 µM CIT before individuals reached free-feeding stage (Csenki et al., 2021). Results showed no mortalities but exposure to 50 µM CIT led to pericardial oedema, blood accumulation, incorrect heart looping, and reduced the size of cardiac chambers.

Short term repeat dose toxicity

49. In a repeat dose study by Jagdale et al. (2020) (according to OECD 407 guidelines) 25 rats of each sex were divided equally into five dosing groups. Animals were treated daily by gavage for 28 days with either a vehicle control (corn oil with 0.4% DMSO) or CIT at 25 µg/kg bw or 100 µg/kg bw. Results showed no abnormal clinical signs during the experimental period. There were no significant histological changes in any of the low dose (25 µg/kg bw) group animals when compared to control animals. Adverse histopathological changes however were observed in the kidney, and the spleen at the high dose (100 µg/kg bw).

Reproductive and developmental toxicity

50. CIT (10 mg/kg feed) was administered orally to pregnant Wistar rats from gestational day (GD) 6-20 (Sharma et al., 2012). Fluorescence activated cell sorter analysis was performed on liver, kidneys and spleen tissue samples of dams, and results showed a significant increase in the percentage of apoptotic cells in liver, kidneys and spleen. Results from the liver and kidney of foetuses showed a significant increase in the percentage of apoptotic cells in kidneys.

51. A study by Li et al. (2023) looked at the effects of CIT on male reproductive toxicity, by exposing rats to 0, 1, 2.5, and 5 mg/kg CIT by gavage from postnatal days (PND) 21-28. At a dose of 5 mg/kg CIT a significant

decreased in serum testosterone levels was observed, while an increase in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels could be seen. In males, LH stimulates Leydig cell production of testosterone and FSH enhances the production of androgen-binding protein by the Sertoli cells which critical for the initiation of spermatogenesis. The authors suggested that CIT inhibits Leydig cell development at multiple levels via different mechanisms with oxidative stress partially playing a role.

Genotoxicity

52. Kuroda et al. (2013) performed three *in vivo* genotoxicity assays in male F344 gpt delta rats: an *in vivo* reporter gene mutation assay using the kidneys, an *in vivo* comet assay, and an *in vivo* micronucleus (MN) assay using the kidneys and bone marrow of F344 rats, respectively. Groups of five rats were administered CIT by gavage at 20-40 mg/kg bw per day for 2-28 days depending on the assay. Results of the *in vivo* reporter gene mutation assay (exposure 28 days) showed no significant increases in gpt or Spi^- mutant frequencies (MF) in DNA extracted from the kidney cortices, suggesting that genomic mutations were not induced. In the comet assay (exposure 2 days), no changes were seen in the kidney cortices, indicating that no DNA damage occurred. The MN assay (exposure 2 days) also showed no significant increase in the micronucleated polychromatic erythrocytes/polychromatic erythrocytes ratio at any dose of CIT. The authors therefore concluded that chromosomal abnormalities or genotoxic mechanisms were not significantly involved in CIT-induced renal carcinogenesis.

Carcinogenicity

53. CIT was administrated at 20 and 40 mg/kg bw day to gpt delta rats by gavage for 28 days to study its proliferative effects in the kidney (Kuroda et al., 2013). Due to decreases in body weight the maximum dose of 40 mg/kg was decreased to 30 mg/kg from day four. Regenerative tubules were observed in the high (40/30 mg/kg bw) dosing group, not in the low dosing

group (20 mg/kg bw group). In the kidney cortex of rats treated with CIT, the labelling index of proliferating cell nuclear antigen (PCNA)-positive cells was significantly increased at all doses compared with that of the control group. The mRNA expression analysis showed increases in *Ccna2*, *Ccnb1*, *Ccne1*, and its transcription factor *E2f1* following treatment with all doses of CIT. The authors therefore concluded that CIT promoted cell cycle progression.

(Sub) Chronic toxicity

Nephrotoxicity

54. In a study by Kumar et al. (2014; abstract only) rabbits were fed with diets containing OTA (0.75 mg/kg feed), CIT (15 mg/kg feed) and OTA + CIT (0.75 and 15 mg/kg feed, respectively) daily, up to 60 days. The results suggested that low concentrations of OTA and CIT either alone or in combination induced apoptosis in a time dependent manner and lipid peroxidation in the rabbit kidney, which according to the authors appeared to play a major role in the pathogenesis of nephrotoxicity.

Reproductive and developmental toxicity

55. A 70-day repeated oral dose toxicity study in female mice was carried out by exposing the animals to 1.25 and 7.5 ppm CIT in drinking water (Hayashi et al., 2012). CIT did not produce any noticeable toxicity in the kidneys, liver, and female genital organs/tracts, except for a slight increase of relative ovary weight. This was followed up with a 90-day repeated oral dose toxicity study, with increased CIT doses of 15 and 30 ppm in drinking water. The results again showed no toxicity in the kidneys, liver, and female genital organs/tracts, except for an increase of both absolute and relative ovary weights accompanied by large follicles at ≥ 15 ppm. On the basis of these findings, the authors determined a lowest-observable-adverse-effect level (LOAEL) of 15 ppm (2.25 mg/kg body weight/day) for CIT.

56. In a one generation study by Singh et al. (2016, abstract only) male and female rats were divided into dosing groups of 1, 3 and 5 ppm CIT in

feed. After 10 weeks male and female rats were mated, and pregnant females were allowed to give birth to offspring (F1 generation) naturally. The offspring were also fed CIT in the above-mentioned doses till the age of 6 weeks and then killed. The authors concluded that the effects of CIT were observed until the F1 generation in a dose-dependent manner and apoptosis and oxidative stress play a role in CIT toxicity. CIT toxicity however did not lead to apoptosis and oxidative stress in male gonads until F1 generation. As only the abstract was available it is not clear how or whether the authors reached the conclusion that effects seen in the F1 generation were a result of exposure of the parent generation, given that offspring were also dosed with CIT.

Human Exposures

Epidemiological studies

57. CIT and DH-CIT have been reported in urine from different human cohorts from Belgium, Czech Republic, Portugal, Germany, Haiti, Bangladesh, Nigeria, Turkey, and Tunisia (Narváez et al., 2021).

58. A study in Nigerian children showed DH-CIT to be present in breastmilk at concentrations of 14.0 –59.7 ng/L. DH-CIT was also measured in the urine of infants who were exclusively breastfed at levels of 5–944 ng/L compared to levels of 5–1,377 ng/L in infants who were not exclusively breastfed (Ezekiel et al., 2022).

59. Three biomonitoring studies were carried out to measure the concentration of CIT and DH-CIT in pregnant women, infants and children in Bangladesh (Ali and Degen, 2020; Kyei et al., 2023, 2022). A provisional daily intake for CIT was calculated and exceeded the level set by EFSA (0.2 µg/kg bw) in 23.3% and 11.9% of children and infants, respectively. CIT was detected in 61% of the urine samples collected from pregnant women (n=447) and dietary exposure to CIT was of public health concern in 16% of the pregnant women. The results of these studies indicated frequent co-exposure to nephrotoxic mycotoxins that varied between the cohorts and regions in

Bangladesh. No evidence was found for an association between higher maternal daily intakes of CIT, and duration of pregnancy, birth weight, birth length, and head circumference at birth. The authors noted that there was large uncertainty regarding the relationship between maternal dietary exposure to CIT and pregnancy loss, preterm birth, born small for gestational age, and small-vulnerable newborns.

60. A study by Narváez et al. (2021) measured CIT and its metabolite DH-CIT in 300 urine samples in the Italian population. CIT was detected in 47% of the samples (n = 300) at concentrations up to 4.0 ng/mg creatinine (Crea) (mean value = 0.29 ng/mg Crea), whereas DH-CIT was detected in 21% of samples (n = 300) up to 2.5 ng/mg Crea (mean value = 0.39 ng/mg Crea). The average exposure to CIT from food ranged from 8% to 40% of the NOAEL in rat for nephrotoxicity (0.2 µg/kg bw per day), set by EFSA (2012), with children being the group with the highest exposure. Four individuals exceeded this NOAEL.

Balkan Endemic nephropathy

61. Balkan endemic nephropathy (BEN) is a familial, slowly progressive, chronic renal disease with insidious onset in the fifth decade of life and terminal renal failure in the sixth or seventh decade (Pavlović, 2013). The pathology of BEN is characterized by a progressive atrophy and sclerosis of all structures of the kidney, and it shares similarities with tubulointerstitial kidney diseases.

62. The occurrence of BEN has been recorded with a high prevalence rate in Serbia, Bulgaria, Romania, Bosnia and Herzegovina and Croatia. The most prominent features of the disease are its endemic nature, the long latency period before development of the disease, familial clustering of the disease and the high incidence of upper urothelial cancer (UUC).

63. Hypotheses relating to the aetiology of BEN include both exogenous (including lead and mycotoxins) and endogenous (including genetic predisposition and viral disease) factors and Pavlović et al. concluded that it is likely multifactorial. The exact aetiology remains unknown.

64. CIT is suspected to be one of the aetiological agents of BEN and CIT-specific DNA adducts were detected in the renal tumours of patients with BEN (Pfohl-Leszkowicz et al., 2007). Studies have indicated that CIT is present in considerable amounts in the diets of people living in Balkan endemic nephropathy areas (Petkova-Bocharova et al., 1991; Vrabcheva et al., 2000).

Exposure

65. Exposure to CIT was determined for women of child-bearing age (16-49 years), using consumption data from the National Diet and Nutrition Survey (NDNS) and occurrence data from the 2014 total diet study (TDS) (Bates et al., 2014, 2016, 2020; Roberts et al., 2018, FSA, 2014).

66. Occurrence data from all food samples analysed for CIT were below the limit of quantification (LOQ) and the exposures calculated are based on the lower bound (LB) and upper bound (UB) values. As the LB is zero for a commodity, it cannot be determined whether a commodity makes a contribution to the overall exposure.

67. Table 1 shows the estimated chronic exposure to CIT. Exposure estimates are presented as the LB and UB of the mean and 97.5th percentile exposures.

68. Mean total exposure to CIT for women of child-bearing age ranges from 0-17 ng/kg bw/day, whilst exposure in high consumers (97.5th percentile) ranges from 0-43 ng/kg bw/day. The food groups with the highest UB values are tea with a mean value of 6.2 ng/kg bw/day and a 97.5th percentile value of

23 ng/kg bw/day; instant coffee with mean value of 2.6 and 97.5th percentile value of 17 ng/kg bw/day; wine with mean value of 1.0 ng/kg bw/day, and 97.5th percentile value of 6.5 ng/kg bw/day.

Table 1: Estimated exposure (in ng/kg bw/day) to CIT from foods consumed by women of childbearing age (16-49 years) using data from the total diet study (Bates et al., 2014, 2016, 2020; Roberts et al., 2018). Exposure shown is as LB to UB.

Food Groups	**Exposure to CIT (ng/kg bw/day) * Mean**	**Exposure to CIT (ng/kg bw/day) * 97.5th percentile**
Alcopops and cocktails	0-0.2	0-1.7
Alternatives to milk	0-0.1	0-0.7
Beer	0-0.7	0-9.4
Branded food drinks	0-0.2	0-2.2
Brown bread	0-0.1	0-0.6
Cider	0-0.3	0-2.9
Cocoa, drinking chocolate	0	0-0.2
Dried fruit	0	0-0.3
Dried pulses	0	0
Fruit juices and vegetable juices	0-0.8	0-4.5
Ground coffee	0-0.1	0-0.3
Herbs and spices	0-0.1	0-0.7
Instant coffee	0-2.6	0-17
Misc cereals Breakfast cereals	0-0.3	0-1.5
Misc cereals Buns cakes and pastries	0-0.3	0-1.5
Misc cereals Chocolate biscuits	0	0-0.4
Misc cereals FLOUR	0	0-0.4
Misc cereals Other cereal products	0-0.1	0-1.4
Misc cereals PASTA	0-0.9	0-3.7
Misc cereals Pizza	0-0.3	0-2.7
Misc cereals RICE	0-0.6	0-3.1
Misc cereals Savoury biscuits	0-0.1	0-0.5
Misc cereals sweet biscuits	0-17	0-0.8
Nuts	0-0.1	0-0.6
Other bread	0-0.3	0-1.6
Snacks	0-0.2	0-1.2
Takeaway Tea	0	0
Takeaway coffee	0-0.2	0-2.0
Tea	0-6.2	0-23
White sliced bread	0-0.4	0-1.8

White unsliced bread	0-0.4	0-1.8
Wholemeal and granary bread	0-0.5	0-2.2
Wine	0-1.0	0-6.5
Total	0-0.7	0-43

*Rounded to 2 significant figures and shown as LB to UB.

LB= Lower bound UB= Upper bound.

69. The carryover of CIT into animal products which is discussed in paragraph 7 is not included in the exposure assessment and would not be expected to significantly add to the exposure under normal, non-experimental, circumstances.

Risk characterisation

70. The available data indicates that CIT is nephrotoxic causing swelling and eventual necrosis of the kidneys. CIT also affects liver function but to a lesser extent. Exposure to CIT has also been associated with reproductive toxicity and teratogenic and embryotoxic effects.

71. EFSA (2012) did not consider the derivation of a HBGV, or application of an MOE approach appropriate for CIT, due to the lack of human dietary exposure data, the available data on genotoxicity and the uncertainties in the database. Instead, EFSA decided to characterise the risk of CIT and determine a level of no concern for nephrotoxicity in humans of 0.2 µg/kg bw per day.

72. EFSA concluded that a concern for genotoxicity and carcinogenicity cannot be excluded at the level of no concern for nephrotoxicity. Limited data on genotoxicity and carcinogenicity has been published since the EFSA evaluation, with the *in vitro* data supporting EFSA's concerns over potential genotoxicity. The new *in vivo* data does not provide evidence for genotoxicity, but there was some indication that CIT promoted cell cycle progression at 40 mg/kg bw in rats.

73. Mean and 97.5th percentile total estimated exposures for CIT were 0-17 and 0- 43 ng/kg bw respectively and are below the level of no concern for nephrotoxicity set by EFSA. Hence, the estimated exposures are not of toxicological concern for nephrotoxicity, but carcinogenicity and genotoxicity cannot be excluded.

74. EFSA did not derive a level of no concern for reproductive or developmental effects. While the data provided evidence for reproductive toxicity, teratogenic and embryotoxic effects of CIT at doses of 1-35 mg/kg bw maternal toxicity, including nephrotoxicity, was also reported. Hence, the reproductive and developmental effects might be secondary to maternal toxicity. A separate study failed to determine the amount of CIT that would cross the placenta, but no metabolites of CIT were detected in the foetus. The doses administered in the available reproductive and development studies were higher than the level of no concern for nephrotoxicity.

75. Studies published since EFSA's evaluation support their conclusion on development and reproductive toxicity, with toxic effects reported in the offspring and dams including nephrotoxicity at doses of 1 mg/kg bw (in feed). Female rats dosed at 0.19-4.5 mg/kg bw (in drinking water) showed adverse effects (LOAEL) at 2.25 mg/kg bw for toxicity in the kidneys, liver, and female genital organs/tracts. (Please note this study was not carried out on pregnant rats).

76. Estimated exposures for CIT in this assessment are also below any doses applied in developmental or reproductive animal studies.

77. The current assessment was based on consumption data from the NDNS for women of maternal/childbearing age and therefore may not be representative of maternal diet. In addition, the NHS recommends that those who are pregnant or planning to become pregnant should not drink alcohol. The inclusion of the UB values for wine, beer, alcopops and cocktails in the

assessment may therefore lead to an over estimation of exposure when considering pregnant women.

78. The current assessment was based on consumption data from the NDNS for women of maternal/childbearing age and therefore may not be representative of maternal diet.

Conclusion

79. Utilising occurrence data from the 2011 TDS for CIT and consumption data for woman of childbearing age from the NDNS, all estimated mean and 97.5th percentile exposures are below the level of no concern for nephrotoxicity set by EFSA in 2012. Hence, estimated exposures are not of toxicological concern for nephrotoxicity. In addition, CIT was not detected above the LOQ in any of the food groups further supporting that exposure to CIT is low.

80. No safe level has been set for reproductive and developmental effects but the studies available report effects at doses higher than the level of no concern for nephrotoxicity. The estimated exposures to CIT do not exceed the level of no concern for nephrotoxicity.

81. Due to the limitations in the database, a risk of genotoxicity and carcinogenicity cannot be excluded.

Questions on which the views of the Committee are sought

82. Members are invited to consider the following questions.

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

I. Do the Committee consider any of the new data to affect the considerations and conclusions by EFSA on the adverse effects of CIT?
II. Do the Committee consider there to be a risk from CIT in the maternal diet?
III. Do the Committee consider the HBGV for nephrotoxicity to be protective of maternal and developmental/reproductive effects?
IV. Do the Committee have any other comments?

Secretariat
October 2024

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

List of Abbreviations and Technical terms

BEN	Balkan endemic nephropathy
bw	Body weight
CIT	Citrinin
COT	Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment
DH-CIT	Dihydrocitrinone
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EFSA	European Food Standards Agency
EU	European Union
FSA	Food Standards Agency
FSH	Follicle stimulating hormone
GB	Great Britain
GD	Gestational day
GP	General Practitioner
HBGV	Health based guidance value
HEK293	Human embryonic kidney 293
hRPTEC	Human renal proximal tubule epithelial cell
LD50	Median lethal dose
LH	Luteinising hormone
LOAEL	Lowest observed adverse effect level
LOQ	Limit of quatification
MF	Mutant frequency
MN	Micronuclei
mRNA	Messenger ribonucleic acid
NI	Northern Ireland
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OTA	Ochratoxin A
PCNA	Proliferating cell nuclear antigen

PND	Postnatal day
ppm	Parts per million
RMR	Red mould rice
RYR	Red yeast rice
SACN	Scientific Advisory Committee on Nutrition
SCE	Sister chromatid exchange
UF	Uncertainty factor

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

References

Abdelhamid, A.M., Dorra, T.M., (1990). Study on effects of feeding laying hens on separate mycotoxins (aflatoxins, patulin, or citrinin)-contaminated diets on the egg quality and tissue constituents. Archives of Animal Nutrition 40, 305–316. DOI: 10.3390/ani11061708

Ali, N., Degen, G.H., (2020). Biological monitoring for ochratoxin A and citrinin and their metabolites in urine samples of infants and children in Bangladesh. Mycotoxin Res 36, 409–417. DOI: https://doi.org/10.1007/s12550-020-00407-7

Anninou, N., Chatzaki, E., Papachristou, F., Pitiakoudis, M., Simopoulos, C., (2014). Mycotoxins' activity at toxic and sub-toxic concentrations: differential cytotoxic and genotoxic effects of single and combined administration of sterigmatocystin, ochratoxin A and citrinin on the hepatocellular cancer cell line Hep3B. Int J Environ Res Public Health 11, 1855–1872. DOI: https://doi.org/10.3390/ijerph110201855

Arai, M., Hibino, T., (1983). Tumorigenicity of citrinin in male F344 rats. Cancer Letters 17, 281–287. DOI: https://doi.org/10.1016/0304-3835(83)90165-9

Bates, B., Lennox, A., Prentice, A., Bates, C., Page, P., Nicholson, S., Swan, G. (2014). National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012) Main heading (publishing.service.gov.uk)

Bates, B., Cox, L., Nicholson, S., Page, P., Prentice, A., Steer, T., Swan, G. (2016). National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014) National Diet and Nutrition Survey (publishing.service.gov.uk)

Bates, B., Collins, D., Jones, K., Page, P., Roberts, C., Steer, T., Swan, G. (2020). National Diet and Nutrition Survey Results from years 9, 10 and 11

(combined) of the Rolling Programme (2016/2017 to 2018/2019) National Diet and Nutrition Survey (publishing.service.gov.uk)

Carlton, W.W., Sansing, G., Szczech, G.M., Tuite, J., (1974). Citrinin mycotoxicosis in beagle dogs. Food and Cosmetics Toxicology 12, 479-IN4. DOI: https://doi.org/10.1016/0015-6264(74)90061-3

Carlton WW and Szczech GM, (1978). Citrinin. In: Mycotoxicoses in Laboratory Animals. Volume 2. Mycotoxic Fungi, Mycotoxins, Mycotoxicoses: An encyclopaedic Handbook. Eds Wyllie TD and Morehouse LG. Marcel Dekker, New York, 371 pp.

Chan, W.H., (2008). Effects of citrinin on maturation of mouse oocytes, fertilization, and fetal development in vitro and in vivo. Toxicology Letters 180, 28–32. DOI: https://doi.org/10.1016/j.toxlet.2008.05.011

Chan, W.H., (2007). Citrinin induces apoptosis via a mitochondria-dependent pathway and inhibition of survival signals in embryonic stem cells, and causes developmental injury in blastocysts. Biochem J 404, 317–326. DOI: https://doi.org/10.1042/BJ20061875

Chan, W.H., Shiao, N.H., (2007). Effect of citrinin on mouse embryonic development in vitro and in vivo. Reproductive Toxicology 24, 120–125. DOI: https://doi.org/10.1016/j.reprotox.2007.04.070

Csenki, Z., Garai, E., Faisal, Z., Csepregi, R., Garai, K., Sipos, D.K., Szabó, I., Kőszegi, T., Czéh, Á., Czömpöly, T., Kvell, K., Poór, M., (2021). The individual and combined effects of ochratoxin A with citrinin and their metabolites (ochratoxin B, ochratoxin C, and dihydrocitrinone) on 2D/3D cell cultures, and zebrafish embryo models. Food and Chemical Toxicology 158, 112674. DOI: https://doi.org/10.1016/j.fct.2021.112674

Degen, G.H., Ali, N., Gundert-Remy, U., (2018). Preliminary data on citrinin kinetics in humans and their use to estimate citrinin exposure based on biomarkers. Toxicology Letters 282, 43–48.

DOI: https://doi.org/10.1016/j.toxlet.2017.10.006

EFSA (2012). Scientific Opinion on the risks for public and animal health related to the presence of citrinin in food and feed. EFSA Journal, 10(7): 2605. DOI: https://doi.org/10.2903/j.efsa.2012.2605

EFSA (2017). Generation of occurrence data on citrinin in food. EFSA Journal, 14(2): 1177E. DOI: https://doi.org/10.2903/sp.efsa.2017.EN-1177

Ezekiel, C.N., Abia, W.A., Braun, D., Šarkanj, B., Ayeni, K.I., Oyedele, O.A., Michael-Chikezie, E.C., Ezekiel, V.C., Mark, B.N., Ahuchaogu, C.P., Krska, R., Sulyok, M., Turner, P.C., Warth, B., (2022). Mycotoxin exposure biomonitoring in breastfed and non-exclusively breastfed Nigerian children. Environ Int 158, 106996. DOI: https://doi.org/10.1016/j.envint.2021.106996

Faisal, Z., Vörös, V., Lemli, B., Derdák, D., Kunsági-Máté, S., Bálint, M., Hetényi, C., Csepregi, R., Kőszegi, T., Bergmann, D., (2019). Interaction of the mycotoxin metabolite dihydrocitrinone with serum albumin. Mycotoxin research 35, 129–139. DOI: 10.1007/s12550-018-0336-z

Foods Standards Agency (2015). Total Diet Study of metals and other elements in food. The Food and Environment Research Agency. FS102081.

Föllmann, W., Behm, C., Degen, G.H., (2014). Toxicity of the mycotoxin citrinin and its metabolite dihydrocitrinone and of mixtures of citrinin and ochratoxin A in vitro. Archives of Toxicology 88, 1097–1107. DOI: 10.1007/s00204-014-1216-8

Hayashi, H., Itahashi, M., Taniai, E., Yafune, A., Sugita-Konishi, Y., Mitsumori, K., Shibutani, M., (2012). Induction of ovarian toxicity in a subchronic oral toxicity study of citrinin in female BALB/c mice. The Journal of toxicological sciences 37, 1177–1190. DOI: 10.2131/jts.37.1177

Hood, R.D., Hayes, A.W., Scammell, J.G., (1976). Effects of prenatal administration of citrinin and viriditoxin to mice. Food and Cosmetics

Toxicology 14, 175–178. DOI: https://doi.org/10.1016/S0015-6264(76)80419-1

Jagdale, P.R., Dev, I., Ayanur, A., Singh, D., Arshad, M., Ansari, K.M., (2020). Safety evaluation of Ochratoxin A and Citrinin after 28 days repeated dose oral exposure to Wistar rats. Regul Toxicol Pharmacol 115, 104700. DOI: https://doi.org/10.1016/j.yrtph.2020.104700

Jeswal, P., (1996). Citrinin-induced chromosomal abnormalities in the bone marrow cells of Mus musculus. Cytobios 86, 29–33.

Kumar, M., Dwivedi, P., Sharma, A.K., Sankar, M., Patil, R.D., Singh, N.D., (2014). Apoptosis and lipid peroxidation in ochratoxin A- and citrinin-induced nephrotoxicity in rabbits. Toxicol Ind Health 30, 90–98. DOI: https://doi.org/10.1177/0748233712452598

Kuroda, K., Ishii, Y., Takasu, S., Kijima, A., Matsushita, K., Watanabe, M., Takahashi, H., Sugita-Konishi, Y., Sakai, H., Yanai, T., Nohmi, T., Ogawa, K., Umemura, T., (2013). Cell cycle progression, but not genotoxic activity, mainly contributes to citrinin-induced renal carcinogenesis. Toxicology 311, 216–224. DOI: https://doi.org/10.1016/j.tox.2013.07.003

Kyei, N.N.A., Cramer, B., Humpf, H.-U., Degen, G.H., Ali, N., Gabrysch, S., (2022). Assessment of multiple mycotoxin exposure and its association with food consumption: a human biomonitoring study in a pregnant cohort in rural Bangladesh. Arch Toxicol 96, 2123–2138. DOI: https://doi.org/10.1007/s00204-022-03288-0

Kyei, N.N.A., Waid, J.L., Ali, N., Cramer, B., Humpf, H.-U., Gabrysch, S., (2023). Maternal exposure to multiple mycotoxins and adverse pregnancy outcomes: a prospective cohort study in rural Bangladesh. Arch Toxicol 97, 1795–1812. DOI: https://doi.org/10.1007/s00204-023-03491-7

Lee, C. H., Pan, T. M., (2010). A 90-D toxicity study of Monascus-fermented products including high citrinin level. Journal of food science 75, T91–T97. DOI: 10.1111/j.1750-3841.2010.01626.x

Li, X., Tian, L., Oiao, X., Ye, L., Wang, H., Wang, M., Sang, J., Tian, F., Ge, R.-S., Wang, Y., (2023). Citrinin inhibits the function of Leydig cells in male rats in prepuberty. Ecotoxicology and Environmental Safety 252, 114568. DOI: https://doi.org/10.1016/j.ecoenv.2023.114568

Meerpoel, C., Vidal, A., Tangni, E.K., Huybrechts, B., Couck, L., De Rycke, R., De Bels, L., De Saeger, S., Van den Broeck, W., Devreese, M., (2020a). A study of carry-over and histopathological effects after chronic dietary intake of citrinin in pigs, broiler chickens and laying hens. Toxins 12, 719.DOI: 10.3390/toxins12110719

Meerpoel, C., Vidal, A., Huybrechts, B., Tangni, E.K., Saeger, S.D., Croubels, S., Devreese, M., (2020b). Comprehensive toxicokinetic analysis reveals major interspecies differences in absorption, distribution and elimination of citrinin in pigs and broiler chickens. Food and Chemical Toxicology 141, 111365. DOI: https://doi.org/10.1016/j.fct.2020.111365

Narváez, A., Izzo, L., Rodríguez-Carrasco, Y., Ritieni, A., (2021). Citrinin Dietary Exposure Assessment Approach through Human Biomonitoring High-Resolution Mass Spectrometry-Based Data. J Agric Food Chem 69, 6330–6338. DOI: https://doi.org/10.1021/acs.jafc.1c01776

Pavlović, N.M., (2013). Balkan endemic nephropathy-current status and future perspectives. Clin Kidney J 6, 257–265. DOI: https://doi.org/10.1093/ckj/sft049

Petkova-Bocharova, T., Castegnaro, M., Michelon, J., Maru, V., (1991). Ochratoxin A and other mycotoxins in cereals from an area of Balkan endemic nephropathy and urinary tract tumours in Bulgaria. IARC Sci Publ 83–87.

Pfohl-Leszkowicz, A., Tozlovanu, M., Manderville, R., Peraica, M., Castegnaro, M., Stefanovic, V., (2007). New molecular and field evidences for the implication of mycotoxins but not aristolochic acid in human nephropathy and urinary tract tumor. Mol Nutr Food Res 51, 1131–1146. DOI: https://doi.org/10.1002/mnfr.200700045

Qingqing, H., Linbo, Y., Yunqian, G., Shuqiang, L., (2012). Toxic effects of citrinin on the male reproductive system in mice. Exp Toxicol Pathol 64, 465–469. DOI: https://doi.org/10.1016/j.etp.2010.10.015

Reddy, R. V., Maruya, K., Hayes, A. W., & Bernd, W. O. (1982a). Embryocidal teratogenic and fetotoxic effects of citrinin in rats. Toxicology 25, 151-160.DOI: https://doi.org/10.1016/0300-483X(82)90026-9

Reddy, R.V., Wallace Hayes, A., Berndt, W.O., (1982b). Disposition and metabolism of [14C]citrinin in pregnant rats. Toxicology 25, 161–174. DOI: https://doi.org/10.1016/0300-483X(82)90027-0

Roberts, C., Steer, T., Maplethorpe, N., Cox, L., Meadows, S., Page, P., Nicholson, S., Swan, G. (2018). National Diet and Nutrition Survey Results from Years 7 and 8 (combined) of the Rolling Programme (2014/2015 – 2015/2016) National Diet and Nutrition Survey (publishing.service.gov.uk)

SACN (2011), The influence of maternal, fetal and child nutrition on the development of chronic disease in later life. SACN_Early_Life_Nutrition_Report.pdf

SACN (2018), Feeding in the First Year of Life. Available: SACN_report_on_Feeding_in_the_First_Year_of_Life.pdf (publishing.service.gov.uk)

Sharma, A., Singh, N., Dwivedi, P., Kumar, M., Telang, A., Patil, R., (2012). Studies on apoptotic changes in combined toxicity of citrinin and endosulfan in pregnant Wistar rats and their fetuses. Toxicol Int 19, 138. DOI: https://doi.org/10.4103/0971-6580.97207

Singh, N.D., Sharma, A.K., Dwivedi, P., Leishangthem, G.D., Rahman, S., Reddy, J., Kumar, M., (2016). Effect of feeding graded doses of citrinin on apoptosis and oxidative stress in male Wistar rats through the F1 generation. Toxicology and industrial health 32, 385–397. DOI: 10.1177/0748233713500836

Singh, N.D., Sharma, A.K., Dwivedi, P., Patil, R.D., Kumar, M., (2008). Experimentally induced citrinin and endosulfan toxicity in pregnant Wistar rats: histopathological alterations in liver and kidneys of fetuses. Journal of Applied Toxicology 28, 901–907. DOI: 10.1002/jat.1354

Singh, N.D., Sharma, A.K., Dwivedi, P., Patil, R.D., Kumar, M., (2007a). Citrinin and endosulfan induced teratogenic effects in Wistar rats. Journal of Applied Toxicology: An International Journal 27, 143–151. DOI: 10.1002/jat.1185

Singh, N.D., Sharma, A.K., Dwivedi, P., Patil, R.D., Kumar, M., (2007b). Citrinin and endosulfan induced maternal toxicity in pregnant Wistar rats: pathomorphological study. Journal of Applied Toxicology: An International Journal 27, 589–601. DOI: 10.1002/jat.1242

Thacker, H. L., Carlton, W. W., & Sansing, G. A. (1977). Citrinin mycotoxicosis in the guinea-pig. Food and Cosmetics Toxicology, 15(6), 553-561. DOI: https://doi.org/10.1016/0015-6264(77)90070-0

Tsai, J. F., Wu, T.S., Huang, Y.T., Lin, W.J., Yu, F.Y., Liu, B.H., (2023). Exposure to Mycotoxin Citrinin Promotes Carcinogenic Potential of Human Renal Cells. J Agric Food Chem 71, 19054–19065. DOI: https://doi.org/10.1021/acs.jafc.3c05218

Vesela, D., Veselý, D., Jelinek, R., (1983). Toxic effects of ochratoxin A and citrinin, alone and in combination, on chicken embryos. Applied and environmental microbiology 45, 91–93. DOI: 10.1128/aem.45.1.91-93.1983

Vrabcheva, T., Usleber, E., Petkova-Bocharova, T., Nikolov, I., Chernozemsky, I., Dietrich, R., Märtlbauer, E., (2000). Citrinin in the diet of young and healthy persons living in balkan endemic nephropathy areas. Mycotoxin Res 16 Suppl 2, 150–153. DOI: https://doi.org/10.1007/BF02940024

Wei, W., Li, C., Wang, Y., Su, H., Zhu, J., Kritchevsky, D., (2003). Hypolipidemic and anti-atherogenic effects of long-term Cholestin (Monascus

purpureus-fermented rice, red yeast rice) in cholesterol fed rabbits. The Journal of Nutritional Biochemistry 14, 314–318.DOI: https://doi.org/10.1016/S0955-2863(03)00051-2