Annex A to TOX/2025/32

Annex A to TOX/2025/32

Introduction and Background

In this guide

In this guide

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

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, among which was the mycotoxin citrinin.

3. The following paper provides the advice of the COT on whether UK exposures to citrinin would pose a risk to maternal health, i.e. maternal outcomes during pregnancy, childbirth and up to 24 months after delivery.

Background

4. Citrinin (CIT) is a mycotoxin produced by several species of fungi of the genera *Aspergillus*, *Penicillium* and *Monascus* and its occurrence is generally due to formation 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.

5. Experimental data indicate that CIT residues may occur in edible tissues and eggs following oral exposure of animals with highly contaminated feed materials (Abdelhamid and Dorra, 1990, Meerpoel et al., 2020a). However, CIT was not detected in edible animal products in the 2014 Total Diet Study (TDS) so the carryover of CIT from feed into animal products has not been considered further in this assessment (FSA, 2014).

6. CIT is also an undesirable contaminant in *Monascus* fermentation products such as red yeast rice (RYR) also known as red mould rice (RMR). RYR is used in Asian cuisine as a food colourant and flavour enhancer and is used in supplements claiming to decrease plasma triglyceride and cholesterol levels (Wei et al., 2003). In 2019, the maximum level (ML) for CIT in RYR preparations was reduced from 2000 µg/kg to 100 µg/kg in Commission Regulation (EC) No 1881/2006 (amendment: Commission Regulation (EU) 2019/1901). The majority

of packaging of RYR supplements state that the product is either not suitable for children and/or women who are pregnant or breast feeding, or, it is recommended these groups should consult a general practitioner (GP) prior to consumption. Due to the presence of warnings on supplement packaging, and the focus of this assessment being on the overall maternal diet, RYR supplements have not been considered further.

Annex A to TOX/2025/32

Toxicology

In this guide

In this guide

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

9. EFSA carried out a full assessment of CIT in 2012 and this has been used as a baseline point for the following hazard characterisation. In addition, a literature search was carried out from 2012-2024, ensuring relevant data published after the EFSA assessment were also considered here. The key studies used in the RIVM risk assessment (2015) were retrieved as part of this literature search. The following sections therefore cover, in brief, all relevant toxicological information up until 2024.

Toxicokinetics

10. The available information on CIT showed it is eliminated predominantly by renal excretion; approximately 75 % of radiolabelled citrinin (14C-citrinin) given to pregnant rats by subcutaneous administration was recovered in urine (Reddy et al., 1982a). A study by Meerpoel et al. (2020b) demonstrated differences in the toxicokinetic properties of CIT between pigs and chickens, including clearance being much slower in pigs than in chickens (Meerpoel et al., 2020b).

11. An *in vitro* study in Chinese hamster lung fibroblast cells demonstrated that the toxic potency of the metabolite DH-CIT was less than CIT (Föllmann et al., 2014) while the interaction of DH-CIT with albumin from different species *in vitro* did not show significant difference between species (Faisal et al., 2019).

12. A study in human volunteers demonstrated that ingested CIT undergoes conversion to dihydrocitrinone (DH-CIT) which is then excreted in the urine along with the remaining parent compound (Degen et al., 2018).

13. A study by Singh (2012) suggested that CIT can cross the placenta (discussed further in the developmental section, see paragraph 31).

Experimental toxicity

Genotoxicity

14. 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 reported in only 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.

15. In vitro assays published since the EFSA opinion showed that CIT induced a dose dependent increase in micronuclei (MN) frequencies, chromosomal aberrations and sister chromatid exchanges (Anninou, 2014; Föllmann, 2014; Tsai, 2023).Tsai et al. (2023) concluded that CIT exposure activated cancer and cell cycle-related signalling pathways when human embryonic kidney 293 (HEK293) cells were treated for 3 and 30 days (Tsai, 2023).

16. *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).

Carcinogenicity

17. F344 rats were fed diet containing CIT in the diet at 0.1 % (estimated to be 0.1 mg/kg bw/day) for 80 weeks; the kidney was identified as the main target organ with reported induction of adenomas (Arai and Hibino, 1983). The first renal tumour was seen at necropsy week 52. Renal adenomas were seen in 35 of the 48 rats that had survived after 40 weeks.

18. A series *of in vivo* studies by Kuroda (2013) administered CIT to rats by gavage at 20-40 mg/kg bw for a maximum of 28 days. The maximum dose of 40 mg/kg was decreased to 30 mg/kg from day four due to decreases in body weight. Regenerative tubules were observed in the kidney cortex in the high dose group, while labelling index of proliferating cell nuclear antigen (PCNA)- positive cells was significantly increased at both doses. The authors suggested that the increase in cyclin encoding genes (*Ccna2*, *Ccnb1*, Ccne1) and its transcription factor (E2f1) indicated induction of cell cycle progression at all tested doses. Cyclin B1 specifically is ubiquitously expressed in humans and plays a key role in controlling the cell cycle transitions.

Nephrotoxicity

19. In vitro, the acute cytotoxic effects of both DH-CIT and CIT were significantly decreased on a Madin-Darby canine kidney (MDCK) cell line, in the presence of albumin (Faisal et al., 2019).

20. In vivo, the acute lethal dose of CIT ranged from 19-134 mg/kg bw depending on species and route of administration (EFSA, 2012). The main changes in pathology following CIT administration were degeneration and necrosis of the kidneys in all species indicating nephrotoxicity. Repeat dose studies assessed by EFSA (2012) confirmed the nephrotoxicity of CIT and highlighted the differences in susceptibility between species, showing guinea pigs and dogs were more sensitive than hamsters. Necropsy showed histopathological changes in the kidneys of all species tested (except hamsters), which were consistent with the acute signs observed.

21. In a study by Lee et al. (2010), CIT was given in the form of fermented

RMR containing different concentrations of CIT (1, 2, 10, 20 and 200 mg/kg). At the highest dose tested (stated by EFSA to be equivalent to 20 µg CIT/kg bw per day) no toxicologically significant alterations in body weight gain, daily feed intake, organ weight and serum biochemistry as well as histopathology of livers and kidneys were observed.

22. A repeat dose study by Jagdale et al. (2020) which treated rats daily by gavage with 25 µg/kg bw or 100 µg/kg bw CIT/day for 28 days reported adverse histopathological changes in the kidney and the spleen at the higher dose. No significant histological changes were reported in animals dosed with 25 µg/kg bw.

23. A 60-day study in rabbits suggested that at low concentrations, CIT (15 mg/kg feed estimated to be 0.45 mg/kg bw/day) 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 (Kumar et al. 2014).

Immunotoxicity and Immunomodulation

24. EFSA concluded in 2012 that the data on immunotoxicity of CIT were incomplete and often non-specific and therefore did not allow for a conclusive evaluation.

25. Since the EFSA opinion, *in vitro* mammalian cell assays reported to show evidence of immunomodulatory and immunotoxic effects of CIT (Sugiyama et al., 2013: abstract only; Islam et al., 2012; Xu et al., 2022) have been published.

26. In vivo, mice treated orally with CIT (1, 5, or 10 mg/kg bw) showed reduced levels of serum immunoglobulin M (IgM) in a dose dependent manner, but no significant changes in immunoglobulin A (IgA),immunoglobulin E (IgE) and immunoglobulin G (IgG). Changes in the regulation of the different immune cell populations were reported in the spleen, mesenteric lymph nodes and small intestine at 1 mg/kg bw. (Islam et al., 2012).

Developmental and reproductive toxicity

27. EFSA considered CIT to show reproductive toxicity with teratogenic and embryotoxic effects based on data from *in vitro* and *in vivo* studies (EFSA, 2012). However, *in vivo* studies also reported maternal toxicity at the same dose, including nephrotoxicity, indicating that the reproductive, teratogenic and

embryotoxic effects of CIT may be secondary to maternal toxicity.

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

29. Since the 2012 EFSA opinion, limited data has been published on the reproductive and developmental effects caused by CIT. However, as the assessment focusses on maternal diet and maternal outcomes, it should be noted that the doses at which these effects were observed in the published studies were in exceedance of EFSA's level of no concern for nephrotoxicity.

30. A repeated oral dose toxicity study by Hayashi et al. (2012) exposed female mice to 0, 1.25 or 7.5 ppm CIT for 70 days in drinking water. No effects on body weight, food consumption or clinical signs were observed and except for a slight increase in relative ovary weight, no other effects on kidney, liver or ovary were observed. A second experiment was carried out exposing female mice to 0, 15 or 30 ppm CIT for 90 days in drinking water. A significant decrease in relative liver weight and decreases in water consumption were observed in the lower (15 ppm) dose group, while decreases in body weight were observed in the higher treatment group (30 ppm). Both absolute and relative ovary weights increased accompanied by large follicles at ≥ 15 ppm (the authors estimated this was equivalent to 2.25 mg/kg body weight/day).

31. Singh et al. (2012) administered CIT (10 mg/kg feed estimated to be 1 mg/kg bw/day) to pregnant rats from gestational day (GD) 6-20, showing a significant increase in the percentage of apoptotic cells in kidneys of dams and foetuses. The effects caused by CIT administration on dams and foetuses were not reported, but toxicity as a result of apoptotic cells in the kidneys was inferred by the authors.

32. In a later one generation study by the same authors (Singh et al. ,2014) male and female rats were administered 1, 3 and 5 mg/kg CIT in feed (estimated to be 0.1, 0.3 and 0.5 mg/kg bw/day)
during mating and during organogenesis. Clinical signs observed included increased water intake, dullness, rough hair coat and polyuria. Mortality was not observed in the dams. Reproductive effects included reduced foetal bodyweight, reduced crown-rump length and increased number of malformations.

33. Newly fertilised zebrafish eggs were exposed to concentrations of 0.78-50 µM CIT before individuals reached free-feeding stage, i.e. while the zebrafish are still embryos prior to reaching the juvenile stage of development. (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.

Epidemiological studies

34. EFSA evaluated two studies in humans (Hetherington, 1941; Ambrose, 1946), however both focussed on inhalation of citrinin powder. EFSA drew no conclusion from these studies, and the effects are not considered to be relevant to the maternal diet.

35. The literature search undertaken here retrieved epidemiological studies specifically on pregnant women following citrinin exposure. However, no studies specific to the UK were available.

36. 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). CIT has also been detected in the breast milk and urine of mothers and the urine of exclusively breastfed infants in two Nigerian communities (Ezekiel et al., 2022).

37. 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). CIT was detected in 61 % of the urine samples collected from pregnant women and dietary exposure to CIT, based on urinary levels, was estimated to exceed the level of no concern for nephrotoxicity set by EFSA (2012) in 16 % of pregnant women. 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.

Health based guidance values

In this guide

In this guide

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.

Exposure Assessment

In this guide

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

49. Exposure to CIT was carried out in the absence of data specific to the maternal diet, and was instead 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).

50. 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.

51. Mean total exposure to CIT for women of child-bearing age ranged from 0-17 ng/kg bw/day, whilst exposure in high consumers (97.5th percentile) ranged

from 0-43 ng/kg bw/day. The food groups with the highest UB values were 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 a mean value of 2.6 and 97.5th percentile value of 17 ng/kg bw/day; wine with a mean value of 1.0 ng/kg bw/day, and 97.5th percentile value of 6.5 ng/kg bw/day.

52. CIT was not detected in edible animal products in the 2014 TDS and the carryover of CIT into animal products could therefore not be included in the exposure assessment.

Risk characterisation

In this guide

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

53. CIT is nephrotoxic but has also been reported to affect liver function. Exposure to CIT has also been associated with reproductive toxicity and teratogenic and embryotoxic effects albeit usually at doses that were maternally toxic. It is therefore uncertain whether these adverse effects were secondary to maternal toxicity.

54. Based on the data available, including data published since the most recent EFSA opinion in 2012, the COT did not think it appropriate to establish a

HBGV but agreed with EFSA's approach of using a level of no concern for nephrotoxicity in humans of 0.2 µg/kg bw per day. Whilst the BMDL of 48 µg/kg bw per day derived by the RIVM was specific to reproductive effects, EFSA's level of no concern is notably lower and would therefore be adequately protective for maternal, reproductive and developmental toxic effects. Any other adverse effects reported after CIT exposure occurred at higher doses.

55. In 2012, EFSA did not consider there to be sufficient data to conclude on the immunotoxic effects of CIT. While some additional data has been published since EFSA's opinion, the database is still very limited and did not allow the COT to draw any conclusions.

56. The available data did not indicate that CIT caused gene mutations, but CIT may have a threshold effect on microtubules and/or spindle assembly. The COT noted that the renal adenomas detected in rats in the Arai (1983) study were uncommon, but the (short) study duration did not allow for firm conclusions to be drawn. Due to the limitations in the database, the COT concluded that a risk of genotoxicity and carcinogenicity cannot be excluded although citrinin showed no evidence of DNA-reactive mutagenicity.

57. 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 of 0.2 µg/kg bw per day set by EFSA. This is also below the BMDL of 48 µg/kg bw per day set by the RIVM based on reproductive effects. Hence, the estimated exposures were not of toxicological concern for nephrotoxicity as well as reproductive and developmental effects.

Uncertainties

In this guide

6. Uncertainties - Annex A to TOX/2025/32
7. Conclusions - Annex A to TOX/2025/32
8. List of Abbreviations and Technical Terms - Annex A to TOX/2025/32
9. References - Annex A to TOX/2025/32

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

58. The following uncertainties and limitations in the assessment were identified:

- The current assessment was based on consumption data from the NDNS for women of maternal/childbearing age (16-49) 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.
- Whilst there was an indication that CIT can cross the placenta (Singh, 2012), there was limited evidence to support this, and hence there remains uncertainty whether CIT can affect the foetus and to what extent.
- RYR as a food additive and/or as a supplement was not considered in this assessment as consumption data was not available and an exposure assessment could not be carried out. However, the majority of packaging of RYR supplements in the UK state that the product was either not suitable for women who are pregnant or breast feeding, or, it was recommended these groups should consult a general practitioner (GP) prior to consumption. In cultures which use RYR as an additive a higher exposure to citrinin may be possible, which may lead to an underestimation in the exposure assessment for certain population groups.
- Different ethnic groups and their specific dietary behaviours have not been characterized, hence there could be an over-or underestimation of exposure.
- Possible additive/synergistic effects with other mycotoxins have not been considered in this assessment. This could lead to an underestimation of the toxicological effects where multiple mycotoxin exposures occur.
- Due to the limitations in the database a risk of genotoxicity and carcinogenicity cannot be excluded. A well-designed toxicological study would be required to further explore the genotoxic and carcinogenic potential of CIT.

- The transfer of CIT from feed to animal products was not considered further in this assessment as CIT was not detected in animal products in the TDS. However, data suggested that transfer can occur, and this could lead to a potential underestimation of exposure, if the occurrence data has changed since the TDS was undertaken.
- It should be noted that the TDS data used to calculate exposure are from 2014 and changes in the prevalence of citrinin may have occurred since then. Dietary patterns may also have changed, for example the increased consumption of plant-based drinks, and vegan/vegetarian diets, which may not be fully represented in the data.

Conclusions

In this guide

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

59. Based on the data available the COT concluded that a HBGV could not be established and agreed with EFSA's approach, using a level of no concern of 0.2 µg/kg bw per day for nephrotoxicity. The COT further considered this level to be adequately protective for maternal, reproductive and developmental effects. The RIVM set a BMDL of 48 µg/kg bw per day as a POD for reproductive effects, which is higher than the level of no concern for nephrotoxicity, adding further

confidence.

60. Estimated exposures for CIT were not of toxicological concern for nephrotoxicity and reproductive and developmental effects. In addition, CIT was not detected above the LOQ in any of the food groups further confirming that dietary exposure to CIT was low and hence supporting the conclusion that levels of CIT in the diet were not of concern to UK consumers.

61. However, due to the limitations in the database a genotoxic and/or carcinogenic risk cannot be excluded. There is a need for further research to explore the potential genotoxic and carcinogenic effects of CIT.

COT Secretariat

September 2025

Annex A to TOX/2025/32

List of Abbreviations and Technical Terms

In this guide

In this guide

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

BMDL	Benchmark dose (lower confidence limit)
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 quantification
MF	Mutant frequency
MN	Micronuclei
mRNA	Messenger ribonucleic acid
NI	Northern Ireland
NOAEL	No observed adverse effect level
NVWA	Netherlands Food and Consumer Product Safety Authority
OECD	Organisation for Economic Co-operation and Development
OTA	Ochratoxin A
PCNA	Proliferating cell nuclear antigen
PND	Postnatal day
ppm	Parts per million
RIVM	National Institute for Public Health and Environment
RMR	Red mould rice
RYR	Red yeast rice
SACN	Scientific Advisory Committee on Nutrition

SCE	Sister chromatid exchange
UF	Uncertainty factor

References

In this guide

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

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

Amberose, A. M., & DeEds, F. (1946). Some toxicological and pharmacological properties of citrinin. **The Journal of Pharmacology and Experimental Therapeutics, 88**(2), 173-186.

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) NDNS Y1 to 4 UK report full text revised February 2017.pdf.

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 NDNS Y 5 6 UK Main Text.pdf.

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.

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 (2014). 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

Hetherington, A. C., & Raistrick, H. (1931). On the production and chemical constitution of a new yellow colouring matter, citrinin, produced from glucose by Penicillium citrinum Thom. **Philosophical Transactions of the Royal Society of London. Series B, Containing Papers of a Biological Character, 220**, 269- 295.

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

Islam, M. R., Roh, Y. S., Cho, A., Kim, J., Kim, J. H., Eo, S. K., ... & Kim, B. (2012). Immune modulatory effects of the foodborne contaminant citrinin in mice. Food and chemical toxicology, 50(10), 3537-3547. DOI: 10.1016/j.fct.2012.06.050

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. A 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

RIVM, NVWA (2015) Assessment of the toxicity of citrinin: Assessment of the toxicity of citrinin.

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.

Sabater-Vilar, M., Maas, R. F., & Fink-Gremmels, J. (1999). Mutagenicity of commercial Monascus fermentation products and the role of citrinin contamination. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 444(1), 7-16. DOI: https://doi.org/10.1016/S1383-5718(99)00095-9

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. SACN report on Feeding in the First Year of Life.pdf.

Singh, N., Sharma, A., 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. Studies on apoptotic changes in combined toxicity of citrinin and endosulfan in pregnant wistar rats and their fetuses - PubMed.

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

Sugiyama, K. I., Yamazaki, R., Kinoshita, M., Kamata, Y., Tani, F., Minai, Y., & Sugita-Konishi, Y. (2013). Inhibitory effect of citrinin on lipopolisaccharide-induced nitric oxide production by mouse macrophage cells. Mycotoxin research, 29, 229-234. DOI: 10.1007/s12550-013-0175-x

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

Xu, R., Shandilya, U. K., Yiannikouris, A., & Karrow, N. A. (2022). Ochratoxin A and Citrinin Differentially Modulate Bovine Mammary Epithelial Cell Permeability and Innate Immune Function. Toxins, 14(9), 640. DOI:10.3390/toxins14090640