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

TOX/2025/27

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

First draft statement 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 meeting, COT agreed that papers on a number of compounds should be prioritised, which included the mycotoxin citrinin.

3. The COT considered the discussion paper on citrinin in the maternal diet (TOX-2024-39) at the October 2024 meeting. At this meeting the Committee requested the addition of any immunotoxicity studies published since 2012.

4. The following paper provides the advice of the COT on whether exposure to citrinin would pose a risk to maternal health. The draft statement (Annex A) includes the COT conclusions on the potential risk in the maternal diet. Studies on the immunotoxicity of CIT published since the last EFSA opinion (2012) were requested by the Committee at the October 2024 meeting and are included as Annex B and have been summarised in the draft statement. Members will recall that this item (as TOX/2025/16) was scheduled for the March 2025 COT meeting but was not discussed due to lack of time. This version of the statement has been revised to address comments received by correspondence after the March 2025 meeting

Questions on which the views of the Committee are sought

5. Members are invited to consider the following questions.

I. Do the Committee have any comments on the content and structure of this statement?
II. Do the Committee have any other comments?

COT Secretariat

July 2025

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TOX/2025/27 Annex A

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

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Introduction

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discussion at the September 2020, COT agreed that papers on a number of compounds should be prioritised, among which was the mycotoxin citrinin. The following paper provides the advice of the COT on whether exposure to citrinin would pose a risk to maternal health.

Background

3. 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.

4. 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).

5. In addition, CIT is 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 preparation 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 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

6. CIT is acutely nephrotoxic in mice and rats, rabbits, pigs and poultry, causing enlargement 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 (EFSA, 2012).

Previous assessments

EFSA 2012 opinion

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

Toxicokinetics

8. 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). Toxicokinetic studies with oral administration of CIT were not available.

Toxicity

9. 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 were degeneration and necrosis of the kidneys in all species indicating nephrotoxicity. 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 the acute signs observed.

Genotoxicity and Carcinogenicity

10. 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.

11. *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).

12. An 80-week feeding study exposed rats to CIT in the diet at initially about 70 mg/kg bw per day; the kidney was identified as the main target organ with reported induction of adenomas (Arai and Hibino, 1983). EFSA concluded that given the observed high incidence of adenomas it cannot be excluded that carcinomas would have occurred if the exposure time had been increased to the full length of a carcinogenicity study (at least two years).

Immunotoxicity

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

Developmental and reproductive toxicity

14. Data from *in vitro* and *in vivo* studies reported reproductive toxicity and teratogenic and embryotoxic effects of CIT (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.

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

Health based guidance value

16. EFSA concluded that the establishment 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.

17. 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. A level of no concern for nephrotoxicity is less secure than a HBGV and is a concentration below which there is no appreciable concern for nephrotoxic effects. This level does not specifically address other end points.

18. 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). In this study, CIT was given in the form of fermented RMR containing different concentrations of CIT (1, 2, 10, 20 and 200 mg/kg) and at the highest dose tested (equivalent to 20 µg CIT/kg bw per day) no toxicologically significant alterations were observed for any dose group. EFSA applied a default uncertainty factor (UF) of 100 for interspecies and interindividual variation.

19. EFSA concluded that a concern for genotoxicity and carcinogenicity could not be excluded at the level of no concern for nephrotoxicity.

Publications since the EFSA 2012 opinion

20. A literature search was undertaken to identify any papers published since the EFSA opinion on CIT in 2012. The following sections summarise the information retrieved from the years 2012-2024.

Toxicokinetics

21. 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). A study in animals 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).

22. The toxicity study by Sharma (2012) (see paragraph 29) indicates that CIT can cross the placenta.

Toxicity

23. 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). In the presence of albumin, the acute cytotoxic effects of both DH-CIT and CIT were significantly decreased on a Madin-Darby canine kidney (MDCK) cell line.

24. A repeat dose study by Jagdale *et al.* (2020) (conducted according to OECD 407 guidelines) which treated rats daily by gavage with CIT (25 µg/kg bw or 100 µg/kg bw) 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. These findings support the NOAEL of 20 µg/kg bw reported by EFSA.

25. A 60-day study in rabbits suggested that at low concentrations, CIT (15 mg/kg feed) 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; abstract only).

Developmental and Reproductive toxicity

26. Since the 2012 EFSA opinion, limited data has been published on the reproductive and developmental effects caused by CIT. The doses at which effects were reported in the published studies were in exceedance of EFSA's level of no concern for nephrotoxicity.

27. A repeated oral dose toxicity study in female mice was carried out by exposing the animals to 1.25, 7.5, 15 and 30 ppm CIT for 70-90 days in drinking water (Hayashi et al., 2012). CIT did not produce any noticeable toxicity at any of the dose levels, except for an increase of both absolute and relative ovary weights accompanied by large follicles at ≥ 15 ppm (authors estimated this was equivalent to 2.25 mg/kg body weight/day).

28. In a one generation study by Singh et al. (2016) male and female rats were administered 1, 3 and 5 ppm CIT in feed for 10 weeks before mating. The offspring were also fed CIT at the same doses until the age of six weeks. The authors concluded that the effects of CIT could be observed until the F1 generation in a dose-dependent manner and that apoptosis and oxidative stress played a role in CIT renal toxicity. CIT toxicity however did not lead to apoptosis and oxidative stress in male gonads including the F1 generation.

29. Sharma et al. (2012) administered CIT (10 mg/kg feed) 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 is inferred by the authors.

30. Newly fertilised zebrafish eggs were exposed to concentrations of 0.78-50 µM CIT before individuals reached free-feeding stage. (Csenki et al., 2021). This is whilst the zebrafish are still embryos prior to reaching the juvenile stage of development. 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.

Genotoxicity

31. *In vitro* assays showed CIT to induce a dose dependent increase in micronuclei (MN) frequencies, chromosomal aberrations and sister chromatid exchanges (Anninou, 2014; Föllmann, 2014; Tsai, 2023: abstract only).

32. A series *of in vivo* studies by Kuroda (2013) in rats administered CIT by gavage at 20-40 mg/kg bw for a maximum of 28 days showed no evidence that chromosomal abnormalities, or genotoxic mechanisms were involved in CIT-induced renal carcinogenesis.

Carcinogenicity

33. 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; abstract only).

34. *In vivo* CIT showed evidence of promoting cell cycle progression when rats were administrated 20 and 40 mg/kg bw day CIT for 28 days (Kuroda et al., 2013). 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 of rats treated with CIT in the high dose group and the labelling index of proliferating cell nuclear antigen (PCNA)-positive

cells was significantly increased at both doses. The mRNA expression analysis showed increases in *Ccna2*, *Ccnb1*, *Ccne1*, and its transcription factor *E2f1* following treatment with all doses of CIT. Authors suggested that this indicated induction of cell cycle progression at all tested doses of CIT.

35. Cyclin B1 (CCNB1 gene) is also a highly conserved cyclin family protein that is ubiquitously expressed in humans, and which is purportedly involved in regulating tumour epithelial–mesenchymal transitions and metastasis. It plays a key role in controlling the G1–S and G2–M cell cycle transitions.

Immunogenicity

36. Limited data was available on the immunotoxicity of CIT since the EFSA opinion in 2012.

37. In *in vitro* mammalian cell assays CIT was reported to show evidence of immunomodulatory and immunotoxic effects (Sugiyama et al., 2013: abstract only; Islam et al., 2012; Xu et al., 2022).

38. *In vivo,* mice treated 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. The authors concluded that CIT has multiple immune modulatory effects in mice that may alter normal functions of immune system and induced T-cell-specific lymphoproliferative capacity (Islam et al., 2012).

Epidemiological studies

39. 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 been detected in the breast milk and urine of mothers and the urine of exclusively breastfed infants (Ezekiel et al., 2022).

40. 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.

41. Overall, the new data published since the 2012 EFSA opinion supports previous findings or adds to the overall knowledge base of CIT. CIT is acutely nephrotoxic, and both *in vitro* and *in vivo* studies have provided provide some evidence that dietary exposure to citrinin mat cause reproductive and developmental toxicity, although most of the effects observed were at maternally toxic doses.

42. The COT agrees 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. The doses administered in the available reproductive and developmental studies were higher than the level of no concern for nephrotoxicity, and so this level would be adequately protective for maternal, reproductive and developmental toxic effects.

Exposure Assessment

43. 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).

44. 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.

45. 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.

46. The carryover of CIT into animal products was not included in the exposure assessment but would not be expected to significantly add to the exposure under normal, non-experimental, circumstances.

Risk characterisation

47. CIT is nephrotoxic, causing enlargement and eventual necrosis of the kidneys, and in some studies was also 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.

48. Based on the data available, including data published since the EFSAs opinion, the COT did not think it appropriate to establish a HBGV but continued to use EFSA’s approach, applying a level of no concern for nephrotoxicity in humans of 0.2 µg/kg bw per day.

49. While a number of studies reported developmental and reproductive toxicity of CIT it is not clear whether these effects might be secondary to maternal toxicity. A study reported by EFSA in 2012 failed to determine the amount of CIT that would cross the placenta, and no metabolites of CIT were detected in the foetus. However, as the doses administered in the available reproductive and developmental studies were higher than the level of no concern for nephrotoxicity, the COT considered the level of no concern for nephrotoxicity to be adequately protective for maternal, reproductive and developmental toxic effects.

50. 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 a conclusive assessment cannot be carried out.

51. The available data demonstrates that citrinin does not cause gene mutations but may have a thresholded effect on microtubules and/or spindle assembly. However, due to the limitations in the database a risk of genotoxicity and carcinogenicity cannot be excluded although citrinin showed no evidence of DNA-reactive mutagenicity.

52. 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 and reproductive and developmental effects, but carcinogenicity and genotoxicity cannot be excluded.

53. 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.

54. 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.

Conclusions

55. Based on the limited data available the COT concluded that a HBGV could not be established and agreed with the continued use of EFSA’s previous approach, using a level of no concern for nephrotoxicity. The COT also considered this level to be adequately protective for maternal, reproductive and developmental effects. However, due to the limitations in the database a risk of genotoxicity and carcinogenicity cannot be excluded.

56. Estimated exposures are 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 is low hence supporting the conclusion that levels of CIT in the diet are not of concern to UK consumers.

Secretariat
October 2024

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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 quantification
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

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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.
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TOX/2025/27 Annex B

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

Annex B: Immunotoxicity

In vitro

1. Sugiyama et al. (2013: abstract only) reported the effect of CIT on nitric oxide (NO) production by a mouse macrophage-like cell line RAW264 activated with lipopolysaccharide (LPS). One of the normal functions of NO is as a pro-inflammatory mediator and it plays a role in the protection from pathogens. LPS-induced NO release from RAW264 cells was inhibited by CIT and the transcription and expression of inducible NO synthase (iNOS) by LPS was suppressed by CIT. The author concludes that CIT may exert adverse effects in macrophages, indicating immunotoxic effects.

2. A study by Xu et al. (2022) investigated the effect of CIT (0, 60, 80, 240 and 270 µmol/L) on barrier and innate immune functions of the bovine mammary epithelium using a bovine mammary epithelial cell line (MAC-T). CIT exposure for 48 h significantly decreased cell viability in a concentration-dependent manner ($p < 0.05$) and IL-6 and TGF-β expression was downregulated ($p < 0.01$). Authors concluded that the results suggest CIT could potentially modulate barrier and innate immune functions of mammary epithelium.

3. In an in vitro experiment by Islam et al. (2012) CIT (1, 5, or 10 µg/ml for 6 hours) inhibited the IL-1β, IL-10, and TNF-α cytokine production in the RAW 264.7 murine macrophage cell line after pre-exposure to different toll-like receptor (TLR) ligands.

Repeat dosing

4. Islam et al. (2012) performed a study in which mice were administered CIT (1, 5, or 10 mg/kg bw) by gavage for 14 days. CIT treatment reduced the level of serum IgM but the production of IgA and IgE was increased in the highest CIT treatment group compared to that of the control group, though this was not considered statistically significant. The IgG level did not change after CIT administration. Administration of CIT changed the regulation of the different immune cell populations in spleen, mesenteric lymph nodes (MLN) and small intestine. Results indicated that CIT induced apoptosis in the spleen, MLN and Peyer's patches (PP) by the change in the ratio of Bax/Bcl-2 activities. To assess the immunocompetence splenocytes and MLN cells from CIT treated mice were stimulated with ConA (T cell mitogen) or LPS (B cell mitogen). An increased proliferative capacity in ConA-induced splenocytes and MLN cells was noticeable in a dose-dependent manner indicating that CIT induced T-cell-specific lymphoproliferative capacity. Authors concluded that CIT has multiple immune modulatory effects in mice that may alter normal functions of immune system.

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