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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of potential risks from mycotoxins in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Patulin

Background

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. The SACN is examining the nutritional basis of the advice. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants, which has been completed, and young children. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

2. In 2014, a request from the European Commission, the European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM Panel) was asked to assess whether patulin (PAT) in food and feed is a potential risk for public and animal health[1], considering the toxicity of PAT and the occurrence in food.

3. A scoping paper (TOX/2015/32[2]) "COT contribution to SACN review of complementary and young child feeding; proposed scope of work for 1-5 year old children" was reviewed by the COT in 2015. A further scoping paper for mycotoxins was presented to the COT in 2017[3].

4. The most recent evaluation of PAT was conducted by Joint FAO/WHO Expert Committee on Food Additives (JECFA) (FAO/WHO, 1995[4]). Prior to that, JECFA evaluated PAT in 1990. In this evaluation, JECFA established a provisional maximum tolerable weekly intake (PMTWI) of 7 µg/kg bodyweight (bw) (FAO/WHO, 1990). The Scientific Committee on Food (SCF), in 1994 agreed with the PTWI of 7 µg/kg bw established by JECFA, in 1990 (SCF, 1994). In 2000, the SCF produced a minute statement[5] and endorsed the provisional maximum tolerable daily intake (PMTDI) of 0.4 µg/kg bw established by JECFA in 1995

[1] https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2014.3916
[2] https://cot.food.gov.uk/sites/default/files/tox2017-15.pdf
[3] https://cot.food.gov.uk/sites/default/files/tox2017-30_0.pdf
[4] https://apps.who.int/iris/bitstream/handle/10665/37246/WHO_TRS_859.pdf;jsessionid=98CAFC5CB9D10C9C7BA763B1B89BDE5F?sequence=1
[5] https://ec.europa.eu/food/sites/food/files/safety/docs/cs_contaminants_catalogue_patulin_out55_en.pdf

(SCF, 2000).

5. Since the JECFA evaluation, no evaluation of PAT has been carried out. Therefore, the COT suggested a review of the recent toxicological data available (*i.e*. 1995 to 2018) and see if this would impact the health-based guidance value (HBGV).

6. This discussion paper presents the findings of a literature survey and review of the recent toxicological data for PAT.

7. The derivation of the HBGVs are detailed and explained. Exposure assessments have been carried out and risk characterisations provided.

8. PAT is a mycotoxin produced by certain species of the genera *Aspergillus* and *Penicillium,* including *A. clavatus, P. expansum, P. patulum, P. aspergillus* and *P. byssochlamys. P. expansum* is a common spoilage microorganism in apples. The major potential dietary sources of patulin are apples and apple juice made from affected fruit (FAO/WHO, 1995).

Toxicokinetics summary

9. From past *in vivo* experimental studies, it was concluded that the major retention sites of PAT are erythrocytes and blood-rich organs (spleen, kidney, lung and liver) (Dailey et al., 1977). From the Dailey *et al.* study, adult rats of both sexes were given a single oral dose of [^{14}C] PAT and were sacrificed at various time intervals from 4 hr to 7 days following administration of the PAT. Two groups of rats were employed; the treated group had been exposed to daily oral doses of unlabelled patulin (dissolved in pH 5.0 citrate buffer) in utero and for 41–66 weeks after weaning, while the controls were given the buffer only throughout gestation and for 38–81 week after weaning. Approximately 49% of the administered ^{14}C radioactivity was recovered from faeces and 36% from urine within 7 days after dosing. Most of the excretion of labelled material occurred within the first 24 hr. All of the ^{14}C activity detected in the urine samples was either metabolites of the original [^{14}C] patulin. About 1–2% of the total radioactivity was recovered as $^{14}CO_2$ from expired air. Carbon-14 radioactivity in various tissues and organs was determined throughout the 7 day period; the most significant retention site was the red blood cells (Dailey *et al.*, 1977).

Mode of action summary

10. Patulin has a strong affinity for sulfhydryl groups which in turn inhibits enzyme activity (Puel et al., 2010). In several studies, it has been concluded that the presence of reactive oxygen species (ROS) and depletion of intracellular glutathione (GSH) is key for PAT mediated toxicity and in turn the main mode of action (Barhoumi et al., 1996., Burghardt et al., 1992, Guo et al., 2013, Ianiri et al., 2016).

Toxicity summary

11. The oral lethal dose (LD_{50}[6]) value of PAT in mice and rats varies from 20–100 mg/kg bw (Pal et al., 2017).

12. The intravenous and intraperitoneal routes are more toxic than the oral route (Pal et al., 2017).

13. Acute studies have shown that PAT causes haemorrhages, formation of oedema and dilation of the intestinal tract in experimental animals (McKinley et al., 1982). In subchronic studies, hyperaemia of the duodenal epithelium and kidney function impairment were observed as the main effects (McKinley et al., 1980).

14. Toxicological data published between 1995 and 2018 reconfirms that dietary exposure of PAT leads to systemic toxicity in the mammalian system including intestinal injury, intestinal ulcers, inflammation, bleeding and a decrease in transepithelial resistance. PAT causes liver inflammation (inducing a rise in alanine aminotransferase (ALT), aspartate transaminase (AST) and malondialdehyde (MDA). PAT also causes detrimental effects on other target organs such as kidneys and thyroids. Cellular and genetic material affects include DNA strand breaks, neuronal degeneration, and degeneration of glomeruli and renal tubules (Song et al., 2014, Mohan et al., 2012, Ayed-Boussema et al., 2012, Maidana et al 2016, Puel et al 2010, Al-Hazmi 2010, de Melo et al 2012). In the 1986 IARC [7] report, it stated that there was inadequate evidence for the carcinogenicity of patulin in experimental animals. This has been restated in a factsheet by the WHO last year which states that: “Patulin is considered to be genotoxic however a carcinogenic potential has not been demonstrated”.[8]

15. The summarised *in vitro/in vivo* toxicological data on organs/tissues/cells and genetic material from 1995 to 2018 can be reviewed in ANNEX A in table format.

16. The summarised studies were selected based on route of administration, quality of the study, cell type, exposure time and concentration.

17. The full comprehensive list of reviewed studies from 1995 to 2018 have been included in ANNEX A under Studies reviewed but not selected as likely to modify the HBGV.

Chemoprevention

18. From reviewing the toxicological literature, it was noted that PAT is of interest again (scientific studies exploring its antimicrobial, antiviral and anticancer compound were done in the mid-1900s) as a chemo preventative/potent anti-cancer activity enhancer, through apoptosis induction in cancer cell lines and even in an *in vivo* model of melanoma cells-bearing mice (Boussabbeh et al 2016, Kwon et al 2012). One recent study showed that PAT exhibited lung cancer chemoprevention, antiproliferative, proapoptotic, and antimigration effects on

[6] LD_{50}: lethal dose at which 50 % of the test population is dead
[7] http://www.inchem.org/documents/iarc/vol40/patulin.html
[8] https://www.who.int/news-room/fact-sheets/detail/mycotoxins

human lung adenocarcinoma cells through inhibition of the Wnt signalling pathway (Monteillier et al 2018).

19. It is possible that in the near future there will be additional *in vivo* experiments and possibly human data.

Health based guidance value (HBGV)

20. The pivotal study used by JECFA (1995) to determine an HBGV was a combined reproductive toxicity, long-term toxicity/carcinogenicity study published by Becci et al., (1981). Concentrations of PAT in citrate buffer of 0, 0.1, 0.5 or 1.5 mg/kg bw/day were administered to groups of 70 FDRL Wistar rats of each sex, by gavage, 3 times/week for 2 years. The rats, derived from the F1 generation showed increased mortality in both sexes at the highest dose. All males had died by 19 months whereas 19% of females survived until termination at 2 years. Body weights of males were reduced at the mid and high dose, but females body weights were comparable in all groups. No difference in tumour incidence was observed. The no-observed effect level (NOEL) in this study was 0.1 mg/kg bw, administered 3 times weekly, equivalent to 43 µg/kg bw/day (FAO/WHO, 1995).

21. Based on this NOEL and with an uncertainty factor (UF) of 100 applied, JECFA established a PMTDI of 0.4 µg/kg bw (FAO/WHO, 1995).

22. It is important to note that genotoxicity data has been published since the HBGV was calculated by JECFA. If the data are conclusive that PAT is genotoxic this would have an impact on the HBGV.

Exposure Assessment

23. This paper has considered exposures based on concentration data measured in the mycotoxins Total Diet Study (TDS) (Stratton *et al.*, unpublished).

24. PAT exposures were calculated using data from the TDS and consumption data from Diet and nutrition survey of infants and young children (DNSIYC) and National Diet and Nutrition Survey (NDNS) (Tables 1a-c). The results from all of the food groups that were analysed for PAT were below the limit of detection (LOD). Individual LODs calculated for the samples analysed ranged from 1.7 µg/kg for the mushroom sample to 13.6 µg/kg for the cereal sample.

25. The mean total lower bounds in all age groups for PAT are zero and thus it is not possible to attribute any food group contributing to total exposure.

26. Mean and 97.5th percentile exposures for infants aged 4 to 12 months ranged from 0 – 0.114 and 0 – 0.293 µg/kg bw/day, respectively. For young children aged 12 to 18 months the mean and 97.5th percentile exposures ranged from 0 – 0.171 and 0 – 0.364 µg/kg bw/day. Calculated mean and 97.5th percentile dietary exposures for young children aged 18 to 60 months ranged from 0 – 0.177 and 0 – 0.324 µg/kg bw/day.

Table 1a. Estimated PAT chronic exposures from the TDS in infants aged 4 to 12 months (µg/kg bw/day)

4 to <6 month-olds (n=116)		6 to <9 month-olds (n=606)		9 to <12 month-olds (n=686)	
Mean	**97.5th percentile**	**Mean**	**97.5th percentile**	**Mean**	**97.5th percentile**
0.000-0.023	0.000-0.099	0.000-0.072	0.000-0.242	0.000-0.114	0.000-0.293

Values rounded to 2 significant figures (SF)

Table 1b. Estimated PAT chronic exposures from the TDS in young children aged 12 to 18 months (µg/kg bw/day)

12 to <15 month-olds (n=670)		15 to 18 month-olds (n=605)	
Mean	**97.5th percentile**	**Mean**	**97.5th percentile**
0.000-0.151	0.000-0.318	0.000-0.171	0.000-0.364

Values rounded to 2 significant figures (SF)

Table 1c. Estimated PAT chronic exposures from the TDS in young children aged 18 to 60 months (µg/kg bw/day)

18 to 24 month-olds (n=118)		24 to 60 month-olds (n=688)	
Mean	**97.5th percentile**	**Mean**	**97.5th percentile**
0.000-0.177	0.000-0.324	0.000-0.164	0.000-0.299

Values rounded to 2 significant figures (SF)

Risk characterisation

27. A JECFA monograph (FAO/WHO, 1995[9]) has been used as the basis for this risk characterisation of PAT.

28. Mean and 97.5th percentile exposures of infants aged 0 to 12 months and young children aged 12 to 60 months (Tables 1a-c) are all below the PMTDI of 0.4 µg/kg bw/day.

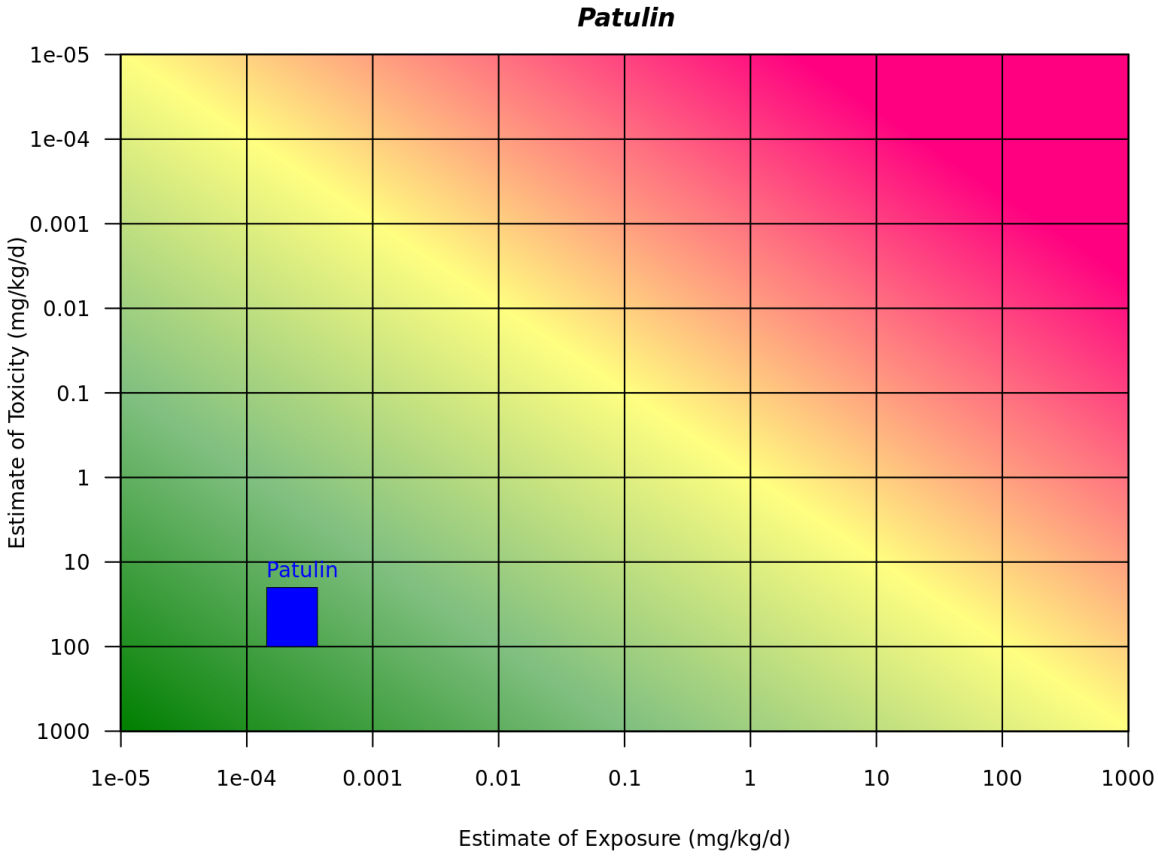
RISK21

29. The RISK21 integrated evaluation strategy is a problem formulation-based exposure-driven risk assessment roadmap that takes advantage of existing

[9] JECFA monograph available at: http://www.inchem.org/documents/jecfa/jecmono/v35je16.htm

information to graphically represent the intersection of exposure and toxicity data on a highly visual matrix.

30. Figure 1 shows a visual comparison of potential exposure and toxicity information using the mean and 97.5th percentile exposure for PAT in the diet of infants aged 0 to 12 months and children aged 1 to 5 years and toxicity information available. PAT sits in the green area (*i.e.* lower end of the exposure scenario) so a low risk.



Conclusions

31. PAT is produced by many different moulds such as *Penicillium*, *Aspergillus*, and *Byssochlamys* species and are mainly produced by *Penicillium patulum* and *Penicillium expansum* commonly found in mouldy apples.

32. In 2000, the SCF produced a minute statement and endorsed the provisional maximum tolerable daily intake (PMTDI) of 0.4 µg/kg bw established by JECFA in 1995 (SCF, 2000).

33. Since the JECFA evaluation, no evaluation into the PMTDI has been done. Therefore, the COT suggested a review of the recent toxicological data available (*i.e.* 1995 to 2018) and see if this would impact the reference dose/HBGV.

34. The summarised *in vitro*/*in vivo* toxicological data on organs/tissues/cells and genetic material from 1995 to 2018 can be reviewed in ANNEX A in table format. Reviewing the toxicity literature data post 1995 to 2018 indicates that it is unlikely that it would lead to modification of the current HBGV, however confirmation is needed that PAT is not genotoxic.

35. The levels of patulin measured in the food groups in the TDS are not of toxicological concern for infants and young children aged 1 to 5 years old.

36. PAT is of interest as a chemopreventive/ potent anti-cancer activity enhancer which if followed up may provide additional data.

37. Questions to be asked of the Committee:

i). Do the Committee agree that there is enough data to conclude on the current status of genotoxicity?

ii). Do the Committee agree that the recent toxicological data is unlikely to impact the HBGV?

iii). Do the Committee have any other comments on this paper?

iv). Do the Committee want a separate statement for PAT or can it be included in the overarching statement?

Secretariat

April 2019

Abbreviations

ALP	alkaline phosphatase
ALT	alanine aminotransferase
bw	bodyweight
CONTAM	Contaminants in the Food Chain
EFSA	European Food Safety Authority
FERA	Food and Environment Research Agency
HBGVs	health based guidance values
JECFA	Joint FAO/WHO Expert Committee on Food Additives
GSH	glutathione
LOD	limit of detection
LD_{50}	lethal dose at which 50 % of the test population is dead
MDA	malondialdehyde
NOAEL	no-observed adverse effect level
PAT	patulin
PMTDI	provisional maximum tolerable daily intake
PMTWI	provisional maximum tolerable weekly intake
TDS	total diet study
ROS	reactive oxygen species
SACN	Scientific Advisory Committee on Nutrition
SCF	Scientific Committee on Food
UF	uncertainty factor
WHO	World Health Organization

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of potential risks from mycotoxins in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Selected toxicity studies (1995-2018)

Toxicological studies of patulin, published between 1995 and 2018, were reviewed. A number of these studies were selected as being relevant to assess whether this recent toxicological data would have an impact on the HBGV established by JECFA. These are separated into tables based on the duration and/or study species/*in vitro* and others.

Table 1 summarises animal studies in which dosing was carried out *via* the oral route/gavage, as this is more relevant to the exposure scenario being considered in this discussion paper and also where effects had been reported.

Table 2 summarises effects on genetic material in animal studies (*via* oral route) and in cells in the likely exposure scenario *via* oral route such as human intestine-colon carcinoma cells, human embryonic kidney cells and human epithelial colorectal adenocarcinoma cells.

Table 3 summarises effects on cells in the likely exposure scenario *via* oral route such as human intestine-colon carcinoma cells, human embryonic kidney cells, human hepatoma cells and human epithelial colorectal adenocarcinoma cells.

Table 1. Effects on organs and tissues

Mode	Dose	Duration	Organism	Organs	Effects	Reference
Gavage	100 µg /kg b.w. every day	60 & 90 days	Rat (Wistor Albino)	Thyroids/Testis	Increased testosterone and LDH levels. Alteration of testis and thyroid morphology. Increase in sperm counts (at 60 days while reduced at 90 days), bent, coiled and sticking of sperm tails, increased lesions, connective tissue and exfoliation of epithelium cells in the epididymis, and stroma expansion in prostate tissue. [Time dependent] (Hormonal imbalance, oedema, fibrosis, Leydig cells hyperplasia)	Selmanoglu et al 2004
Gavage	100 µg/kg b.w. every day	60 & 90 days	Rat	Gonads	Decreased sperm count Alteration in sperm morphology	Selmanoglu et al 2006
Oral	100 µg/ kg /b.w. per day	2-3 weeks	Male mice	Liver	Liver enlargement, inflammation, granulation	Gashlan (2008)

					in the hepatocyte cytoplasm, nucleus elongation, and cellular necrosis, increased ALP, AST, ALT, LDH, and LPO	
Oral	100 µg /kg/ b.w. per day	60 & 90 days	Male rats	Thymus capillary	Swollen endothelial cells, increased width of the basement membrane of endothelial cells, closed capillary lumen, accumulation of fibrous material at the periphery of the capillary, and nuclear anomalies	Gül et al. (2006)
Oral	100 µg /kg/ b.w. per day	60 & 90 days	Male rats	Thymus interdigitating dendritic cells (IDCs)	Development of irregular nuclei, nuclear degradation, perinuclear electron-lucent zone, chromatin margination and condensation, loss of cristae in mitochondria, increased number of lysosomes and apoptotic bodies	Özsoy et al. (2008)
Gavage	100 µg /kg/ b.w. per day	60 & 90 days	Wistar albino male rats	Thyroid	Formation of lesions, infiltration of lymphoid cells, follicles enlargement of interstitial tissue, and degenerated colloid	Selmanoğlu and Koçkaya (2004)
Gavage	100 µg /kg/ b.w. per day	60 & 90 days	Wistar albino male rats	Testes	Formation of lesions, oedema, and fibrosis in interstitial tissue, epithelium disorder in seminiferous tubule, cell debris in the seminiferous tubule lumen and hyperplasia in local Leydig cells	Selmanoğlu and Koçkaya (2004)
Gavage and intraperitoneal injection	100 µg /kg/ b.w. per day for 3 days	1-2 weeks	Male BALB/c mice	Liver	Necrosis in hepatocytes, infiltration of inflammatory cells, the formation of focal hepatocellular vacuolation, and slight haemorrhaging.	Jayashree et al. (2017)

Table 2. Effects on genetic material

Organism	Mode	Concentration/Treatment time	Changes in the nucleus, chromosome and gene/DNA/RNA	Reference
human intestine -colon carcinoma (HCT116) and human embryonic kidney cells (HEK293)	i.p.	5–25 µM [0.7706-3.853 µ/ml] 24hr	Increased chromosome aberrations and DNA damage (Nrf2/ SIRT3)	Boussabbeh et al. (2015)
Male CF-1 mice	i.p.	1.0–3.75 mg/kg/ b.w. (i.p) (single dose) for 3 hours.	Induced DNA strand breaks in brain, liver, and kidneys	De Melo et al. (2012)
Male rats	oral	0.1 mg/kg/ b.w. per day 60 & 90 days	Expansion of the nucleus, loss, and clumping of chromatin, and formation of pyknotic nuclei	Gül et al. (2006)
human embryonic kidney cells (HEK293) Mouse Embryonic Fibroblasts (MEF) C57BL/6 wild-type (mouse) p53 knockout mice	cells	7 µM for cell line and 2.5 mg/kg bw for mice for 1hr, 3hr, 6hr or 12 h	Induced DNA damage	Jin et al. (2016)
human epithelial colorectal	cells	50 µM [7706 µg/L]	Suppressed density-enhanced phosphatase-1 (DEP-1) [plays a	Katsuyama et al. (2014)

adenocarcinoma (Caco-2)		[7.706 µg/ml] 6hr and 12hr	recognized prominent role as a tumour suppressor] and PPARγ (peroxisome proliferator-activated receptor gamma) [regulates fatty acid storage and glucose metabolism]	
Chinese hamster lung fibroblasts (V79)	cells	0–1 µM [0.15412 µg/ml] 3, 4.5 hr and 6hr	DNA damage by cross-linking, delayed cell cycle, reduced cell proliferation, the formation of micronucleus, multipolar mitotic	Glaser & Stopper, 2012

Table 3. Effects on cells

Cell line name	Concentration/ Time	Changes in cells	Reference
HCT116-human colon carcinoma HEK293-human embryonic kidney cells	0–30 µM [0-4.624 µg/ml] 24 hr	Increased cytotoxicity and ROS production	Boussabbeh et al. (2015)
HL-60 human promyelocytic leukaemia HEK293 human embryonic kidney cells	0–10 µM [0-1.5412 µg/ml] 6 hr	Accumulation of intracellular ROS and plasma membrane blebs [PAT can trigger mitochondria-dependent apoptosis through a p53-independent pathway, which is governed by attacking cellular thiol-containing molecules and increasing ROS generation]	Wu et al. (2008)
Caco-2: human intestinal epithelial cells PBMC: peripheral blood mononuclear cells moDCs human blood monocyte-derived dendritic cells	50 µM [7.706 µg/ml] 5hr,10hr,20hr,25hr	Reduced cell viability, maturation, and TER (PAT exposure on the human GI tract) [T cell proliferation was highly sensitive to PAT with major effects for concentrations above 10 nM]	Assunção et al. (2016)
human hepatoma cells (HepG2)	0–80 µM [6164.8 µg/ml] 1hr	DNA damage through strand breaks [PAT induces DNA strand breaks in HepG2 cells] [The DNA strand breaks are associated with the formation of ROS and depletion of GSH, suggesting that the DNA strand breaks induced by PAT probably depend on the ROS-induced oxidative DNA damage, and GSH, as a main intracellular antioxidant, plays a vital role in defence against PAT-induced DNA damage]	Zhou et al. (2010)

Key

ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
IDCs	interdigitating dendritic cells
GI	gastrointestinal tract
LDH	lactate dehydrogenase
LPO	lipid peroxidation
ROS	reactive oxygen species
TER	transepithelial resistance

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Table 4. Effects on organs and tissues (Toxicity studies 1995-2018)

Patulin concentration (kg bw)	Mode of administration	Organism	Organs/tissues	Changes in organs/tissues	References
152.5 µg/ kg per day*	Oral	Male mice MFI strain	Kidneys	Degeneration of renal corpuscles, Bowman's capsules, kidney tubules and glomeruli; haemorrhage and extravasations in tubules of the cortical region; hyper-cellularity in glomeruli, and medullary tissue; and flaking out of the epithelial cells [lipid peroxidation] [protein oxidation]	Al-Hazmi (2014)
152.5 µg/ kg per day*	Oral	Male mice MFI strain	Liver	Necrosis, dilated sinusoids, damaged and loosened endothelial cells, induction of apoptosis, the formation of a pyknotic centric nucleus, karyorrhexis, megalonuclei, and karyolysis nuclei in hepatocytes (ALP, AST, ALT)	Al-Hazmi (2014)
3.75 mg	Intraperitoneal injection	BALB/c female mice	Cardiac tissue	Increased triglycerides, cholesterol, protein carbonyl, LPO, and MDA	Boussabbeh et al. (2015)
3.75 mg	Intraperitoneal injection	BALB/c female mice	Liver and kidneys	Increased carbonyl protein, MDA, and LDH and decreased GSH/GSSG ratio	Boussabbeh et al. (2016)
1.0–3.75 mg	Intraperitoneal injection	Male CF-1 mice	Brain, liver, urinary bladder and kidneys	Increased LPO and reduced GSH	De Melo et al. (2012)
10 µM	Intramuscular injection	M91 rabbits (male and female)	Bones	Increased the density of cortical bone, lack of primary vascular longitudinal bone, accelerated remodelling of bone, reduced secondary osteons, the appearance of the osteons near the periosteum, and enhanced width of the osteonal vascular canals	Duranova et al. (2015)
0.2 mg	Subcutaneous injection	Adult albino male rats	Kidneys	Shrinkage and hyper-cellularity of glomeruli, wall destruction, infiltration of interstitial inflammatory cells, hyperplasia of epithelial lining, apical aggregation of organelles, loss of microvilli, mitochondria, basal infoldings, and parallel arrangement of mitochondria, formation of cellular cast and wide lumens, partial loss of the brush border of proximal and distal convoluted tubules, and irregular heterochromatic formation in the nucleus	El-sawi et al. (2015)
5–25 µg/mL	–	Maize seedlings	Shoot and root	Increased activity of APX, GR, DHAR, and MDHAR and reduced GST	Ismaiel and Papenbrock (2017)

Patulin concentration (kg bw)	Mode of administration	Organism	Organs/tissues	Changes in organs/tissues	References
2.5 mg	Intraperitoneal injection	C57BL/6 wild-type and p53 knockout mice	Kidney tissues	No obvious pathological changes were found in the kidneys	Jin et al. (2016)
10 µg	Intramuscular injection	Male rabbits meat line M91 (Californian broiler line)	Femoral bones	Increased the density of cortical bone, lack of primary vascular longitudinal bone, accelerated remodelling of bone, reduced the secondary osteons, the appearance of the osteons near the periosteum, enhanced width of the osteonal vascular canals	Kováčová et al. (2015)
0.08–2.56 mg	Oral	Female B6C3F1 mice	Liver, spleen, thymus, kidneys, adrenals, and lungs	No changes in body and organ weights	Llewellyn et al. (1998)
6 µM [924.72 µg/L]	Intraperitoneal injection	BALB/c mice	Liver and kidneys	Oedema in the hepatic lobule, inflammation in tubule, vacuolar degeneration, induction of protein casts in renal tubules and increased serum AST, ALT, urea, and LDH	Lu et al. (2017)
10–100 µM [1541.2-15412 µg/L]	–	Male crossbred piglets	Jejunal tissue	Induced necrosis in apical villi, cellular disruption, and decreased number of goblet cells in villi and crypts	Maidana et al. (2016)
350 and 3.5 mg/L	Luminal application	Rats	Stomach lumen	Reduced GSH level	Rychlik et al. (2004)
40–160 µg/animal	Dermal exposure/topical application	Swiss albino mice	Skin	G1 and S-phase cell cycle arrest, and induction of apoptosis	Saxena et al. (2009)
400 nmol	Topical application	Female Swiss albino mice	Cutaneous tissue	The absence of papillomatous growth and tissues with normal epidermis and dermis cells	Saxena et al. (2011)
1 mg	Intraperitoneal injection	Male Kunming mice	Liver	Elevation of ROS, TBARS, and decreased GSH level; SOD and CAT activities reduced	Song et al. (2014)
1 mg	Intraperitoneal injection	Male Kunming mice	Bone marrow	The increase of micronucleus, MNPCE, MNNCE, chromosome aberrations, gaps, and breaks	Song et al. (2014)

**N.B.* the control group was given saline whereas the PAT group was administered in apple juice

Table 5. Effects on cells (Toxicity studies 1995-2018)

Cell line name	Patulin concentration	Changes in cells	References
MNBN: cytokinesis-blocked human lymphocytes V79: Chinese hamster lung fibroblasts	0.8 µM [123.296 µg/L]	Increased cytotoxicity	Alves et al. (2000)
HepG2-human hepatoma cells	5–100 µM [770.6 µg/L-15412 µg/L]	Decreased cell viability, and increased ROS generation	Ayed-Boussema et al. (2013)
HCT116-human colon carcinoma HEK293-human embryonic kidney cells	5–25 µM [770.6-3853 µg/L]	Increased cytotoxicity, ROS, LPO, and MDA	Boussabbeh et al. (2015)
CHO-K1-Chinese hamster ovary cells	0.2–25 µM [30.824-3853 µg/L]	Reduced cell viability, increased ROS and MDA production	Ferrer et al. (2009)
MMV-Luc-oestrogens TARM-Luc-androgens and progesterone TM-Luc-progestogens TGRM-Luc-glucocorticoids and progestogens H295R-human adrenal cortex	0.0032–32 µM [0.493184- 4931.84 µg/L]	Reduced cell viability, increased oestradiol and progesterone (at 500 ng/mL); reduced testosterone and progesterone (at 5000 ng/mL)	Frizzell et al. (2014)

Cell line name	Patulin concentration	Changes in cells	References
Male rat thymus capillary endothelial cells	0.1 mg	Loss of cytoplasm, cell organelles, mitochondrial cristae, and nuclear irregularities	Gül et al. (2006)
HaCaT-human keratinocyte cells 293T-epithelial embryonic kidney	0–7 µM [0-1078.84 µg/L]	Increased the ROS, and inhibition of autophagy	Guo et al. (2013)
HEK293 human embryonic kidney cells MEF-mouse embryonic kidney cells	7 µM [0-1078.84 µg/L]	Induced the ROS and LPO, decreased the GSH level and activity of CAT	Jin et al. (2016)
Caco-2 human intestinal epithelial cells	50 µM [7706 µg/L]	Decreased TER potential	Kawauchiya et al. (2011)
CHO-K1 Chinese ovary hamster cells HPBL human peripheral blood lymphocytes cells HEK293 human embryonic kidney cells	0–2.5 µM [0-385.3 µg/L]	Decreased cell viability	Liu et al. (2003)
HEK293 human embryonic kidney cells HL-60-human promyelocytic leukemia CHO-K1 Chinese ovary hamster cells	100 µM [15412 µg/L]	Increased intracellular ROS, LPO, and LDH release	Liu et al. (2007)
HEK293 human embryonic kidney cells HL-60-human promyelocytic leukemia CHO-K1 Chinese ovary hamster cells	0–100 µM [0-15412 µg/L]	Increased intracellular ROS, LDH, MDA, and LPO	Liu et al. (2007)
HEK293 human embryonic kidney cells AML-12 epithelial hepatocyte	6 µM [0-924.72 µg/L]	Increased ROS and cytotoxicity	Lu et al. (2017)
PBMC peripheral blood mononuclear cells	0–100 ng/mL	Inhibition of cell proliferation, and depletion of intracellular GSH	Luft et al. (2008)
HT-29-D4 – human colon epithelial Caco-2 human intestinal epithelial cells	100 mM [15412 µg/L]	Decreased of TER and cell viability, increased LDH release, no effect on sugar absorption and chloride secretion.	Mahfoud et al. (2002)
Caco-2 human intestinal epithelial cells	100 µM [15412 µg/L]	Decreased TER potential, and no cytotoxicity	McLaughlin et al. (2009)
V79 Chinese hamster lung fibroblasts	10 µM [1541.2 µg/L]	Increased cytotoxicity	Pfeiffer et al. (1998)
HEK293 human embryonic kidney cells	0–100 µM [0-15412 µg/L]	Increased cytotoxicity and intracellular ROS, and depleted GSH level	Pillay et al. (2015)
Female Swiss albino mice skin cells	400 nmol	Enhanced ROS generation, decreased free sulfhydryls, CAT, SOD, and GR activities	Saxena et al. (2011)
V79 chinese hamster lung fibroblasts	0–1.2 µM [184.944 µg/L]	Depleted GSH, G2-M arrest, and mutation in HPRT	Schumacher et al. (2005)
J774.1 mouse macrophage cells NeHepLxHT morphology of primary fetal liver cells RAW 264.7 mouse leukemic monocyte macrophage cells	0–100 µM [0-15412 µg/L]	Reduced cell viability, NO, and GSH	Tsai et al. (2016)
PBMC peripheral blood mononuclear cells	0.3–1000 ng/mL	Reduced the PBMC and IFN-γ producing T cell viability, and cytokine production	Wichmann et al. (2002)
HEK293 human embryonic kidney cells PBMCs peripheral blood mononuclear cells MDCK Madin Darby canine kidney cells	5–50 µM [770.6- 7706 µg/L]	Increased cytotoxicity, and LDH release	Wu et al. (2005)
HepG2 human hepatoma cells	0–60 µM [0-9247.2 µg/L]	Increased the DNA migration, intracellular level of ROS and 8-OHdG formation, and a decrease in intracellular GSH level	Yang et al. (2011)
HEK293 human embryonic kidney cells	2.5–15 µM	Increased intracellular ROS and MDA, reduced the GSH, cell viability, induced apoptosis, and mitochondrial membrane potential collapse	Zhang et al. (2015)

Cell line name	Patulin concentration	Changes in cells	References
	[385.3 - 2311.8 µg/L]		
HEK293 human embryonic kidney cells	8 µM [1232.96 µg/L]	Reduced cell viability, intracellular ATP and mitochondrial membrane potential; induced ROS and LDH generation, and LDH	Zhong et al. (2017)
HepG2 human hepatoma cells	0–0.75 µM [0-115.59 µg/L]	Depleted GSH level	Zhou et al. (2009)
HepG2 human hepatoma cells	0–80 µM [0-12329.6 µg/L]	Increased ROS, LPO, 8-OHdG and decreased GSH	Zhou et al. (2010)
Saccharomyces cerevisiae	50 µM [7706 µg/L]	Reduced cell viability and increased the proteasome	Guerra-Moreno and Hanna (2017)

Table 6. Table of effects on genetic material (Toxicity studies 1995-2018)

Organism/cell line name	Patulin concentration	Changes in the nucleus, chromosome, and gene/DNA/RNA	References
cytokinesis-blocked human lymphocytes (MNBN) Chinese hamster lung fibroblasts (V79)	0.8 µM [123.296 µg/L]	Induction of chromosomal abbreviation and formation of micronucleus	Alves et al. (2000)
Tissue cells (HepG2)	5–100 µM [770.6- 15412 µg/L]	Increased DNA damage	Ayed-Boussema et al. (2013)
Male CF-1 mice	1.0–3.75 mg	Induced DNA strand breaks in brain, liver, and kidneys	De Melo et al. (2012)
detection of oestrogens (MMV-Luc) androgens and progestagens (TARM-Luc) progestagens (TM-Luc) glucocorticoids and progestagens (TGRM-Luc) adrenocortical cell line (H295R)	0.0032–32 µM [0.493184-4931.84 µg/L]	Antagonistic property on nuclear receptor transcriptional activity	Frizzell et al. (2014)
Chinese hamster lung fibroblasts (V79)	0–1 µM [0-154.12 µg/L]	DNA damage by cross-linking, delayed cell cycle, reduced cell proliferation, the formation of micronucleus, multipolar mitotic spindles and nucleoplasmic bridge, centrosome amplification, and induced kinetochore-negative cells	Glaser and Stopper (2012)
Saccharomyces cerevisiae	50 µM 7706 µg/L	Splicing of HAC1 mRNA not induced	Guerra-Moreno and Hanna (2017)
*Sporobolomyces*strain IAM 13481 and *Rhodosporidium kratochvilovae* strain LS11	5 and 50 µM	Proteins involved in oxidation-reduction and transport processes were upregulated, and synthesis and modification of proteins, ion transports, cell division and regulation of cell cycle were repressed	Ianiri et al. (2016)
Saccharomyces cerevisiae (S288C)	50 ppm	490 genes expressed and 447 genes repressed	Iwahashi et al. (2006)
colon cancer proliferation and corresponding inhibitors (HCT116) colon adenocarcinoma (SW620) human epithelial colorectal adenocarcinoma (Caco-2)	0–10 µM [1541.2 µg/L]	Increased ATF3 mRNA expression	Kwon et al. (2012)
Chinese hamster ovary- epithelial cell line (CHO-K1) Human Peripheral Blood Lymphocytes (HPBL) human embryonic kidney cells (HEK293)	0–2.5 µM [385.3 µg/L]	Induced sister chromatid exchange, oxidative DNA damage, DNA gap and break, and no effect on the hOGG1 and HSP70 mRNA expression	Liu et al. (2003)
Chinese hamster lung fibroblasts (V79)	10 µM [1541.2 µg/L]	Fragmentation of the acentric chromosome, cell cycle arrest, and formation of micronuclei	Pfeiffer et al. (1998)
human embryonic kidney cells (HEK293)	0–100 µM [15412 µg/L]	Increased expression of *SOD2*, *CAT* and *GPx* genes	Pillay et al. (2015)
Swiss albino mice	40–160 µg/animal	Excessive DNA damage, and cell cycle arrest at G0-G1 and S-phase	Saxena et al. (2009)

Organism/cell line name	Patulin concentration	Changes in the nucleus, chromosome, and gene/DNA/RNA	References
Chinese hamster lung fibroblasts (V79)	0–1.2 µM [184.944 µg/L]	The G2-M phase of cell cycle arrest and a mutation in the *HPRT* gene	Schumacher et al. (2005)
Chinese hamster lung fibroblasts (V79)	0.5–2.5 µM [77.06 µg/L]	Induced DNA–DNA cross-links, DNA strand breaks, and oxidative DNA modifications	Schumacher et al. (2006)
Male Kunming mice	1 mg/kg bw	Increased micronucleus, MNPCE, MNNCE, chromosome aberrations, gaps and breaks	Song et al. (2014)
monocyte macrophage (J774.1) morphology of primary fetal liver cells (NeHepLxHT) mouse leukemic monocyte macrophage cells (RAW 264.7)	0–100 µM [0-15412 µg/L]	Expression of p62, Nrf2, TRAF6 and LC3 mRNA and suppression of IL-6, TNFα, IL-1β, and IFNβ mRNA	Tsai et al. (2016)
Primary Peripheral Blood Mononuclear Cells (PBMC)	0.3–1000 ng/mL	IL-4 over expression and IFN-γ repressed	Wichmann et al. (2002)
human embryonic kidney cells (HEK293) Primary Peripheral Blood Mononuclear Cells (PBMC) Madin-Darby Canine Kidney (MDCK)	5–50 µM [770.6 7706 µg/L]	Induced DNA damage, upregulated *EGR-1* gene, regulation of *c-Fos*, *JunB*, *Gapd*, and *FosB* genes not affected	Wu et al. (2005)
human embryonic kidney cells (HEK293)	0–10 µM [1541.2 µg/L]	Increased chromatin condensation, nuclear fragmentation, DNA laddering, and hypodiploid DNA regions	Wu et al. (2008)
human embryonic kidney cells (HEK293)	2.5–15 µM [385.3 2311.8 µg/L]	Formation of chromatin condensation and nuclear fragmentation	Zhang et al. (2015)
human embryonic kidney cells (HEK293)	8 µM [1232.96 µg/L]	Downregulated gene expression of Bcl-2, ATP6, ATP8, and NDUFA4 and upregulated gene expression of SDHA, Bax, p53, caspase 9, 3, 6, and 7	Zhong et al. (2017)
human hepatoma cells (HepG2)	0–0.75 µM [0-115.59 µg/L]	Induced the formation of binucleate, multinucleate and micronuclei cells	Zhou et al. (2009)

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