

The potential risks from ergot alkaloids in the maternal diet: Discussion paper

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, fetal 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 horizon scanning item at the January 2020 meeting with a scoping paper being presented to the Committee of Toxicity (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 COT meeting in September 2020, it was agreed that papers on a number of components should be prioritised. For this paper, the advice of the COT is sought on whether exposure to ergot alkaloids

(EAs) would pose a risk to maternal health.

Background

3. Ergot alkaloids (EA) are secondary metabolites produced by the fungi families Clavicipitaceae and Trichocomaceae, with *Claviceps purpurea* being the most widespread *Claviceps* species in Europe. They are known parasites affecting more than 400 plant species, including some economically important cereal grains such as rye, wheat, triticale, barley, millet and oats.

4. There are 80 different naturally occurring EAs (Schiff, 2006). Based on their occurrence and the available toxicological data the European Food Safety Authority (EFSA) considered six EAs in their risk assessment in 2005, namely: ergotamine, ergocornine, α -ergocryptine, ergosine, ergocristine (peptide ergot alkaloids) and ergometrine (a lysergic acid amide). EFSA further included both forms (-ine and inine) in their assessment, while the -inine forms are considered biologically inactive interconversion occurs under various conditions (EFSA, 2005, Tasker and Wipf, 2021). Bromocriptine is a synthetic ergoline derivative and it is used in the treatment of Parkinson's disease and pituitary tumours (Herdman et al., 2001).

Toxicity

5. The latest EFSA opinion (2012), was used as a starting point for the current assessment. Literature searches were conducted using PubMed and Scopus; the search terms are shown in Appendix A.

6. Due to their structural similarities, EAs are suggested to be agonists or antagonists of noradrenaline, dopamine and serotonin neurotransmitters (Arroyo-Manzanares et al., 2017, Fitzgerald and Dinan, 2008). EAs have been reported to produce direct peripheral effects such as uterotonic action or vasoconstriction, indirect peripheral effects such as serotonin antagonism or adrenergic blockade, and central nervous system (CNS) effects such as induction of hypothermia and emesis (EFSA, 2012).

Toxicokinetics

7. Data from the literature suggest that EAs are absorbed from the gastrointestinal (GI) tract and subjected to oxidative biotransformation, primarily by cytochrome P450 3A4 via hydroxylation in the liver. Although cytochrome

P450 3A4 metabolizes EAs via hydroxylation, EAs have also been shown to bind to it as an inhibitor substrate. Furthermore, cytochrome P450 3A4 is involved in the biosynthetic pathway of EAs in *Claviceps purpurea* (Haarmann et al., 2006). Recent studies have shown that many EAs are derivatives of lysergic acid (LA) and that P450 monooxygenase and its cluster CloA plays a key role in its biosynthesis. (Gerhards et al., 2014, Haarmann et al., 2006; Mulac and Humpf, 2011).

8. Following hepatic metabolism, biliary excretion represents the main elimination pathway in primates including humans (Althaus et al., 2008, EFSA, 2012). However, there is less faecal excretion in cattle, possibly due to a ruminant specific absorption profile. For example, limited information available from experimental studies in cattle showed that approximately 96 % of EAs were excreted in urine (Stuedemann et al., 1998).

9. No studies are available on the toxicokinetics of dietary EAs in humans. However, human data are available on ergotamine used as a pharmaceutical to treat Parkinson's disease. Absorption of ergotamine from the GI tract is poor after oral/sublingual administration and bioavailability is further reduced by high pre-systemic hepatic metabolism. Ergotamine tartrate can also be given rectally, to improve absorption, yet bioavailability is still $\leq 5\%$. Caffeine can be included in oral and rectal preparations to improve the absorption, the efficacy of this is however still unclear (Tfelt-Hansen et al., 2000; Silberstein and McCrory, 2003).

Acute Toxicity

10. In vivo studies identified different sensitivities of EAs in various animals, with rabbits being the most sensitive species with LD50 values between 0.9 and 3.2 mg/kg bw (intravenous injection).

11. The LD50s were determined in a series of experiments by Griffith et al. (1978) on naturally occurring and (semi-) synthetic EAs administered by intravenous (i.v.), subcutaneous (s.c.) and oral exposure (in 2 % gelatine) in mouse, rat and rabbit. Following administration, the animals were observed for 7 days and all the clinical signs, including mortality, were recorded. All naturally occurring EAs demonstrated a low oral acute toxicity compared to the i.v. and oral administrations (Table 1), supporting the observations of low absorption and high pre-systemic metabolism via the oral route. Rabbits were the most sensitive species. Based on the LD50s, EAs exhibit a moderate oral acute toxicity (EFSA, 2012).

Table 1: LD50s in mice, rats and rabbits by i.v. or oral exposure for EAs.

Substance Species Route LD50 (mg/kg)

D-lysergic acid	Mouse	i.v.	240
	Rabbit	i.v.	100
Ergometrine	Mouse	i.v.	160
	Mouse	Oral	460
	Rat	i.v.	120
	Rat	Oral	671
	Rabbit	i.v.	3.2
	Rabbit	Oral	27.8
Ergotamine	Mouse	i.v.	265
	Mouse	Oral	3200
	Rat	i.v.	38
	Rat	Oral	1300
	Rabbit	i.v.	3
	Rabbit	Oral	550
Ergosine	Mouse	i.v.	33.5
	Rat	i.v.	30
	Rabbit	i.v.	1.23

Ergostine	Mouse	i.v.	125
	Mouse	Oral	1700
	Rat	i.v.	47
	Rat	Oral	>1000
	Rabbit	i.v.	1.2
	Rabbit	Oral	~1000

i.v.: intravenous

12. An acute toxicity study by Griffith et al. (1978) identified ergometine as the least toxic and ergocryptine as the most toxic compound. However, repeat oral dose studies in rats demonstrated no significant differences in the toxicity of ergotamine, ergometrine and α -ergocryptine, with no-observed-adverse effect levels (NOAELs) ranging from 0.22 - 0.60 mg/kg bw per day (EFSA, 2012).

13. In humans, acute effects are directly related to receptor antagonism and include diarrhoea, collapse, and vomiting. Exposure to EA contaminated cereal grains, can also lead to a condition called ergotism (Guggisberg, 2003). There are two main types of ergotism, gangrenous and convulsive. The two distinct types of ergotism may be considered as acute and chronic varieties. The gangrenous form is caused by the strong vasoconstrictive properties of some EAs, which result in restriction of blood flow to parts of the body (ischemia). As a result, parathesis (tingling) is felt in fingers and toes followed in many cases by dry gangrene of the limbs and consequently loss of limbs. In the convulsive form, tingling is followed by neurotoxic symptoms such as hallucinations, delirium, and epileptic-type seizures. It has been suggested that a deficiency in vitamin A together with high concentration of EAs could be a causative factor inducing convulsive ergotism (Arroyo-Manzanares et al., 2017; EFSA, 2012). Additional symptoms of ergotism are lethargy or depression.

14. Limited data are available for individual EAs and their toxic effects on human cells. Most data consist of receptor interaction analysis for single substances in dopamine over-expressing cells or tumour cells. As an example, studies by Larson et al. (1995,1999) indicated that ergocryptine, ergocristine, ergotamine, ergonovine, ergovaline, and ergocornine increased baseline dopamine of about 30 μ M. No toxic effects were shown in the studies.

15. Because EAs act on several neurotransmitter receptors, particularly adrenergic, dopaminergic and serotonergic receptors, EFSA considered neurotoxicity the main acute effect with symptoms such as restlessness, miosis or mydriasis, muscular weakness, tremor and rigidity (see the Section 24 on neurotoxicity).

Chronic toxicity

Humans

16. No data were available on the chronic toxicity of EAs from dietary exposure in humans. However, limited information was available from the use of ergot containing medications. Case studies on long-term use of EA medication for migraine headaches reported severe lower extremity claudication (pain in the limbs) due to chronic arterial insufficiency (Garcia et al., 2000; Bogun et al., 2011; Fröhlich et al., 2010; Silberstein and McCrory, 2003). In all instances treatment was discontinued and patients were also asked to discontinue the use of caffeine and cigarettes. Anti-platelet therapy was used to successfully reverse the symptoms.

17. As noted above, ergotamine is used for the treatment of acute migraine. To minimize toxicity and avoid adverse effects such as nausea, vomiting, weakness, muscle pains, paraesthesiae and coldness of the extremities, the dosage is limited to no more than 10 mg per week (Orton and Richardson, 1982; Perrin et al., 1985). Bromocriptine is a synthetic compound with an affinity to dopamine receptors due to its structural similarities to a variety of EAs. It is therefore used as a treatment for Parkinson's disease and type II diabetes. However, several studies with 790 patients in total, showed adverse side effects in 37 % of severe Parkinson's patients at dose up to 100 mg/day (Lieberman et al., 1985; Bernard et al., 2015).

Animals

18. A study by Valente et al. (2020) has shown that EAs are structurally similar to biogenic amines, such as 5-hydroxytryptamine (serotonin), which allows them to interact with serotonin receptors as a response to chronic exposure and act as agonists or antagonists when consumed by bovine. In contrast, an earlier study by Kalkman et al. (1982) showed vasoconstriction based on adrenergic-like receptors in rats injected intravenously with ergometrine.

19. A study by Korn et al. (2014) reported spontaneous alopecia, erosions, crusts and necrosis, specifically of the tail area in rabbits from a colony which was originally used in an approved breeding experiment. The lesions were found exclusively in young rabbits aged 113 ± 20 days (14 out of 103 rabbits) fed with hay and a commercial pelleted feed. Immunoassays on blood samples showed mean and maximum EA concentrations of $410 \mu\text{g}/\text{kg}$ and $1,700 \mu\text{g}/\text{kg}$, respectively. In addition, EAs were detected in the faeces of the affected rabbits at levels up to $200 \mu\text{g}/\text{kg}$. The mean and maximum dietary intakes of total EAs were 17 and $71 \mu\text{g}/\text{kg}$ bw, respectively. Other toxins, such as fusarium toxin, were also detected in the feed, but at levels which, according to the authors, did not explain the observed effects.

Genotoxicity and Carcinogenicity

20. Data on the genotoxic and mutagenic effects of EAs are limited and the information available was contradictory. EFSA (2012) considered the available genotoxicity studies to be insufficient, except for ergotamine and concluded that the available data on ergotamine did not indicate any mutagenic potential; though conflicting reports of chromosome damaging effects in vitro. In a review by Uelger et al. (2020) it was noted that ergotamine was not mutagenic in mouse lymphoma cells but sister chromatid exchange had been observed in Chinese hamster ovary cells.

21. A study by Roberts and Rand (1977) indicated that ergotamine induced chromosomal abnormalities in human lymphocytes and leukocytes. In a further study by Dighe and Vaidya (1988) ergotamine, ergonovine and methylergonovine effectively induced sister chromatid exchange (SCE) frequencies in vitro cultured Chinese hamster ovary (CHO) cells, while ergocristine and α -ergocryptine showed a weak and no effect, respectively.

22. No genotoxicity or mutagenic effects in the *Salmonella typhimurium* (St) and mouse lymphoma TK+/- assay were demonstrated in a recent study on ergotamine tartrate (Et) (Seifried et al., 2006). Et was tested at the dose of 10-10000 $\mu\text{g}/\text{plate}$ in the St assay; Et was incubated on plates containing St at 5 different concentrations for 48h at 37 C. In the mouse lymphoma TK+/- assay, Et was tested at the concentration of 7.7-108 $\mu\text{g}/\text{mL}$ for 4h (Seifried et al., 2006).

23. EAs are not considered carcinogenic and have not been classified by the International Agency for Research on Cancer (IARC). However, they are being studied as possible cytostatic agents (De Ruyck et al., 2015). Experiments in rodents showed that ergotamine, ergocryptine and ergocornine were able to

suppress the growth of pituitary tumours in vivo (MacLeod and Lehmeyer, 1973). More recently a vast range of mRNA microarray studies investigated the cytotoxic activity on a range of human cancer cell types and reported strong inhibitory effects for 1-propylagroclavine and dihydroergocristine against genes associated with the progression of leukaemia. Further information is required to confirm the cytotoxic effect pathway, but preliminary results suggest that EAs have the potential to be used as possible treatment of otherwise drug-resistant and refractory tumours via the inhibition of prolactin release from the anterior pituitary gland (Cassady et al., 1974; Mrusek et al., 2015).

Neurotoxicity

24. EFSA concluded that EAs induce neurotoxicity in mammals, with symptoms such as restlessness, miosis or mydriasis (contraction and dilation of the pupils), muscular weakness, tremor and rigidity. Repeated dosing with various EAs, resulted in ischaemia, particularly in the extremities (e.g., tails) of rats, decreased body weight gain and changes in the levels of some hormones. Tail gangrene was observed in rats 5 - 7 days after a single i.p. exposure to 25 mg/kg bw ergotoxine (a mixture including ergocornine, α - and β -ergocryptine, and ergocristine) (Griffith et al., 1978). The no-observed-adverse effect levels (NOAELs) was 0.22 - 0.60 mg/kg bw per day. No major quantitative difference in the toxicity of ergotamine, ergometrine and α -ergocryptine was observed (EFSA, 2012).

Reproductive and Developmental toxicity

Animals

25. Limited information was available on the effects of EAs exposure during pregnancy, in particular the effects on the vascular system supporting the growing fetus. A study by Duckett et al. (2014) examined fetal growth during maternal exposure to ergot alkaloids during gestation. Pregnant ewes (n = 16) were randomly assigned to one of two dietary treatments: (1) endophyte-infected (*N. coenophialum*) tall fescue seed (E+; 0.8 ug of ergovaline/g diet DM) and (2) endophyte-free tall fescue seed (E-; 0.0 ug of ergovaline/g diet DM). The results of the study demonstrated that exposure to EAs during mid and/or late gestation in ewes reduced fetal growth. A more recent study in ewes by Klotz et al. (2019) indicated that maternal blood supply to the placenta appeared to be shielded from adverse effects of EAs, but umbilical vasculature was not, which could adversely influence the normal fetal growth.

26. Studies in livestock also reported reduced reproductive performance, particularly in female cattle, after EAs exposure (Poole and Poole, 2019). A regional vasoconstriction and corresponding decreased blood flow to reproductive tissues was observed, along with a decreased dry matter intake, and/or increased body temperature, leading the authors to conclude that the effect of EAs was both direct and indirect.

27. In utero exposure to EAs in pregnant ewes, especially during phase two of gestation, alters fetal growth, muscle fibre formation, and miRNA expression (non-coding micro RNA that is associated with the control of gene expression, specifically glucose transport, insulin signalling, intracellular ATP, hypertension, or adipogenesis) (Greene et al., 2019). Ergovaline was shown to be a potent vasoconstrictor in the bovine umbilical and uterine arteries and reduces blood flow to developing placental tissues and fetuses (Klotz et al., 2015). Placental weight reduction is highly correlated with fetal birthweight and high exposure to EAs in ruminants can result in additional adverse effects such as hyperexcitability, hypermetria, and tremors (Klotz et al., 2015, Britt et al., 2019).

28. Several studies have reported effects of EAs on the reproductive process in rodents and stallions, including prevention of pregnancy predominantly by poor sperm quality, interference with implantation, and embryotoxicity. Page et al., 2019 ; reported an in vitro study on bovine sperm in which sperm morphology and motility was adversely affected by incubation with three different EAs- ergotamine, dihydroergotamine and ergonovine. Fayrer-Hosken et al., 2013 reported that consumption of high levels of EAs decreased the gel free volume of sperm samples in stallion but did not result in statistically significant on the spermiogram (a test of fertility). These studies on adverse reproductive effects in males have been included for completeness.

Humans

29. In a randomised clinical trial to evaluate the effects of EAs on milk secretion postpartum, 30 women received an injection of 0.2 mg methylergobasine immediately after delivery followed by 3 tablets of 1 mg of ergotamine tartrate given daily (orally) for 6 days post-partum. Results showed that the treatment had no significant effect on either the weight of the infant or the quantity of milk consumed (Jolivet et al., 1978). A study by Arroyo-Manzanares et al (2017) addressed the similarities of the actions of EAs to those of monoamine neurotransmitters and provided evidence that EAs have the ability to act on the secretion of adrenocorticotrophic hormone (ACTH), prolactin (PRL), luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Prolactin has an

important biological function in lactation, reproduction, immune responses, and metabolism and inhibition of milk production due to the inhibition of prolactin has been seen in humans, laboratory animals, and livestock animals (Arroyo-Manzanares et al., 2017; Prendiville et al., 2000).

30. In utero exposure to the EA derivative methylergonovine has been associated with a case report of sirenomelia. Sirenomelia is a rare and deadly condition characterized by fusion of the lower limbs, lower spinal column defects, severe malformations of the urogenital and lower GI tract, and an aberrant abdominal umbilical artery. An alteration in the development of the caudal portion of the mesoderm (Duesterhoeft et al., 2007; Garrido-Allepuz et al. 2011) or an alteration of the growth of the umbilical vessels, with corresponding inadequate blood supply to the caudal portion (Cozzolino et al., 2016) has been suggested as reason for this congenital malformation at the critical stage of organogenesis.

31. Data from trials on the use of EAs (ergometrine and methylergometrine) as uterotonic medication suggested that EAs may decrease mean blood loss from both mother and child by at least 500 mL and increase maternal haemoglobin levels in the blood. However, the results also suggested the treatment increased the incidence of adverse effects such as increased blood pressure and pain after birth (Liabsuetrakul et al., 2018).

32. An epidemiological study linked the use of purified ergotamine to congenital abnormalities during pregnancy in humans. Ergotamine was used to treat migraine and a mean daily dose of 1.5 mg ergotamine during the 2nd month of pregnancy led to a higher risk for neural-tube defects, spina bifida, posterior cleft palate, congenital cataract and clubfoot (Czeizel, 1989). Two further case studies have reported an association between the use of ergotamine during early pregnancy and the development of Möbius sequence in children (Smets et al., 2004; Graf and Shepard, 1997). Möbius sequence is a rare congenital disorder defined by the paralysis of the 6th and 7th cranial nerves in combination with various odontological, craniofacial, ophthalmological and orthopaedic conditions (Kjeldgaard Pedersen et al., 2017). Vascular disruption has been suggested as one possible explanation for the pathogenesis of Möbius sequence. Ergotamine has also been reported to cause vasospasm and a prolonged and marked increase in uterine tone (Smets et al., 2004; Graf and Shepard, 1997).

33. Interrogation of the UK Teratology Information Service database did not identify any information related to EAs.

Health-based guidance values

34. EFSA (2012) considered the vasoconstrictive effect the critical effect for EAs, based on the finding of tail muscular atrophy in rats fed for 13 weeks with ergotamine. A BMDL10 of 0.33 mg/kg bw per day was derived and an uncertainty factor (UF) of 3 was applied to account for deficiencies in the database. Together with the default uncertainty factor of 100 for intra- and interspecies differences, EFSA applied an overall UF of 300 and established an acute reference dose (ARfD) of 1 µg/kg bw (rounded to one significant figure). In line with EFSA's recommendations, an additional UF of 2 was applied for the extrapolation from a sub-chronic to a chronic study in their derivation of the tolerable daily intake (TDI). Therefore, an overall UF of 600 was applied to the same BMDL10 of 0.33 mg/kg bw per day to establish a TDI of 0.6 µg/kg bw per day. EFSA concluded that the available data were not sufficient to determine the relative potencies of individual EAs, but the limited data available for some EAs showed no apparent differences in potencies.

35. In 2021, the Joint FAO/WHO Expert Committee on Food Additives (JEFCA), identified ergotamine maleate as the cause of uterine contractions in humans during late pregnancy and postpartum and decided to investigate the role of EAs in the diet (JEFCA, 2021). As ergometrine has the highest uterotonic effect and potency for uterine contractions JECFA established an ARfD based on the lowest oral therapeutic dose of 0.2 mg ergometrine maleate (equivalent to 2.5 µg/kg bw, expressed as ergometrine). An UF of 2 was applied for extrapolating a pharmacological LOEL to a NOEL. JECFA also applied an UF of 3.16 to account for possible interindividual toxicodynamic differences. Applying a composite UF of 6.3 (2 × 3.16) an ARfD of 0.4 µg ergometrine/kg bw was derived. JECFA also considered two 4-week studies on ergotamine tartrate and α-ergocryptine in rats and derived a reference point (BMDL10) of 1.3 mg/kg bw, based on muscular degeneration in the tail. However, JECFA considered the human pharmacological effect level of 2.5 µg/kg bw and resulting NOEL to provide a much more sensitive reference point than a downstream toxic effect in animals. A TDI of 1 µg/kg bw per day was initially established by selecting the lowest BMDL10 value of 0.6 mg/kg bw per day. However, JECFA concluded that a TDI should not be higher than the ARfD and hence decided to establish a group TDI for the sum of total EAs in the diet at the same value as the group ARfD of 0.4 µg/kg bw per day.

Sources of EA exposure

36. EFSA's Comprehensive European Food Consumption Database refers mainly to processed food and data available on human dietary exposure to EAs derived from consumption estimation are very limited. EFSA's estimated chronic dietary exposure in the adult population varied between 0.007 and 0.08 µg/kg body weight (bw) per day for average consumers and 0.014 and 0.19 µg/kg bw per day for high consumers. The acute dietary exposure in the adult population ranged between 0.02 and 0.23 µg/kg bw per day for average consumers, and between 0.06 and 0.73 µg/kg bw per day for high consumers. The highest exposure (chronic and acute) was in countries with relatively high consumption of rye bread and rolls. Assessment of the dietary exposure to EAs in specific groups of the population indicated no significant differences between vegetarians and the general population. However, a slightly higher dietary exposure to EAs was noted in consumers of unprocessed grains compared to the general population (EFSA, 2012).

37. Caraballo et al. (2019) reported concentrations of up to 47 µg/kg in grains and grain-based composites. In cereal and flour, particularly rye, EA concentrations of over 7 mg/kg (Krska and Crews, 2008) have been reported.

38. The European Union (EU) established maximum levels (ML) of ergot sclerotia and EAs, effective as of January 2022. For milled products derived from barley, wheat, spelt or oats with an ash content of less than 900 mg/100 g, an EAs limit of 100 µg/kg applies, being further reduced to 50 µg/kg in July 2024. For the same types of grain products with a higher ash content or sold directly to the end consumer, the maximum level of EAs was set at 150 µg/kg. The maximum level of EAs in wheat gluten is 400 µg/kg. As an open pollination species, rye is generally more susceptible to infestation, which is accounted for by a higher maximum level. Milled rye products are subject to an EAs limit of 500 µg/kg, further reduced to 250 µg/kg in July 2024. A maximum level of 20 µg/kg for EAs in grain-based food for infants and toddlers has also been introduced.

39. The German Federal Institute for Risk Assessment (BfR) based their risk assessment on the consumption of rye flour contaminated with ergotamine and ergometrine. The BfR estimated that on average, ergotamine accounted for a maximum of 46 % of the total alkaloid content. The consumption of 250 g of the most contaminated rye flour would result in an intake of 834 µg ergotamine per day per person. The consumption of highly contaminated rye flour therefore exceeds the maximum therapeutic daily dose tolerated for a month-long therapy of 670 µg ergotamine tartrate per day (BfR, 2004).

40. A research group at the University of Ghent (Arroyo-Manzanares, 2017) carried out an extensive survey on European products and tested 1,065 samples of cereals and cereal products (rye, wheat, and multigrain-based food that contain rye and wheat) intended for human consumption. In total, 59 % of samples tested positive for EAs, with EAs present in 84 % of rye, 67 % of wheat and 48 % of multigrain-based food. The levels ranged from 1 to 12,340 µg/kg.

41. Storm et al. (2011) detected EAs in rye flour samples from Danish mills with an average and maximum concentration of 46 µg/kg and 234 µg/kg, respectively. Crews et al. (2007) detected EAs in 25 of 28 samples, including all 11 types of rye crispbreads with concentration up to 340 µg/kg while Müller et al. (2009) found EAs in 92 % of the tested rye products with a maximum content of 740 µg/kg. Reinhold et al. (2011) tested 500 food samples from Germany, approximately 50 % were positive for EAs with a highest concentration of 1,063 µg/kg. A more recent survey by Bryła et al. (2015) detecting EAs in 83 % of the tested rye grain, 94 % of rye flour, and 100 % of rye bran and flake samples. Ergocryptine, ergocristine, and ergotamine, including their C8-isomers, were the most common EAs detected in the majority of surveys and foods sampled.

42. A study by Dusemund et al. (2006) concluded that ergometrine contributed 5 % of the total alkaloid content and that consumption of 250 g of the most contaminated rye flour would result in an intake of 91 µg ergometrine per day per person. This would be below the lowest therapeutic dose equivalent to 400 µg ergometrine hydrogen maleate per day.

Exposure Assessment

43. Exposure to EAs were derived using data from the 2014 Total Diet Study-Mycotoxin analysis and consumption data from the National Diet and Nutrition Survey (NDNS).

44. The TDS data (Stratton et al., 2017) was based on 28 food groups which were further divided to produce 49 food groups; all food groups in which EAs were detected and hence included in this assessment can be seen in Table 2 (for all food groups included in the survey, please see Annex B, Table 5). Total EAs and epimers (ergocristine, ergotamine, ergocornine, ergosine, ergocryptine, ergometrine, ergocristinine, ergotaminine, ergocorninine, ergosinine, ergocryptinine and ergometrinine) were determined by LC/MS/MS (Carbonell-Rozas et al., 2021). Those twelve EAs are the most frequent forms detected. More data on each specific subset are available in the Diet Study (TDS) – Mycotoxin Analysis Report, 2017 [Diet Study \(TDS\) – Mycotoxin Analysis: Final report](#)

food.gov.uk

Table 2: Foods groups considered

Food groups

White sliced bread

White unsliced bread

Brown bread

Wholemeal and granary bread

Other bread

Misc cereals FLOUR

Misc cereals Buns cakes and pastries

Misc cereals Savoury biscuits

Misc cereals Sweet biscuits

Misc cereals Chocolate biscuits

Misc cereals Breakfast cereals

Misc cereals RICE

Misc cereals Other cereal products

Misc cereals PASTA

Misc cereals Pizza

45. The food groups contributing most to EAs exposure were a) wholemeal and granary bread, b) white sliced bread and c) other bread. Mean and 97.5th percentile estimated exposure to EAs from the individual food groups for women of child-bearing age (16- 49 years) can be found in Table 3 (acute) and Table 4 (chronic).

Table 3: Acute exposure to ergot alkaloids in women of childbearing age; food groups not containing EAs have been removed.

Food groups	Exposure (µg/kg bw)	Exposure (µg/kg bw)
	LB - UB	LB - UB
	Mean	P97.5
White sliced bread	0.0092-0.0093	0.041-0.041
White unsliced bread	0.0060-0.0061	0.034-0.035
Brown bread	0.0023	0.033
Wholemeal and granary bread	0.024	0.091
Other bread	0.015	0.068
Misc cereals FLOUR	0.0015-0.0017	0.012-0.013
Misc cereals Buns cakes and pastries	0.0019-0.0027	0.0094-0.013

Misc cereals Savoury biscuits	0.00091-0.00093	0.0076-0.0077
Misc cereals Sweet biscuits	0.0015-0.0016	0.0084-0.0090
Misc cereals Chocolate biscuits	0.00056-0.00061	0.0054-0.0058
Misc cereals Breakfast cereals	0.003562-0.00359	0.0183-0.0184
Misc cereals RICE	0-0.0062	0-0.025
Misc cereals Other cereal products	0.00097-0.0017	0.0088-0.015
Misc cereals PASTA	0.0022-0.0065	0.0089-0.027
Misc cereals Pizza	0.0072-0.0075	0.054-0.056
Total	0.052-0.057	0.12-0.13

LB= lower bound; UB= upper bound.

Table 4: Chronic exposure to ergot alkaloids in women of childbearing age; food groups not containing EAs have been removed.

Food groups	Exposure (µg/kg bw)	Exposure (µg/kg bw)
	LB - UB	LB - UB
	Mean	P97.5th percentile
White sliced bread	0.0040-0.0041	0.02140-0.021479

White unsliced bread	0.0021-0.0021	0.012761-0.01291
Brown bread	0.00080	0.010
Wholemeal and granary bread	0.011	0.052
Other bread	0.0055	0.029
Misc cereals FLOUR	0.00055-0.00062	0.0047-0.0052
Misc cereals Buns cakes and pastries	0.00067-0.00092	0.0038-0.0052
Misc cereals Savoury biscuits	0.00033-0.00033	0.003059-0.003125
Misc cereals Sweet biscuits	0.00057-0.00061	0.0036-0.0039
Misc cereals Chocolate biscuits	0.00018-0.00020	0.0018-0.0019
Misc cereals Breakfast cereals	0.00189-0.00190	0.0089-0.0090
Misc cereals RICE	0-0.0024	0-0.012
Misc cereals Other cereal products	0.00029-0.00052	0.0028-0.0048
Misc cereals PASTA	0.00071-0.0021	0.0035-0.010
Misc cereals Pizza	0.0019-0.0020	0.015-0.015

Total

0.031-0.035

0.072-0.080

LB= lower bound; UB= upper bound.

Exposures in subpopulation groups

Vegans and Vegetarians

46. The number of vegans and vegetarian among the total number of consumers (n= 2556) were relatively small with 112 and 10, respectively.

47. The LB and UB mean and 97.5th percentile acute exposures were 0.064 – 0.070 µg/kg bw and 0.127 – 0.13 µg/kg bw for vegans, respectively. For vegetarians the LB and UB mean and 97.5th percentile exposures were 0.061 – 0.067 µg/kg bw and 0.135 – 0.14 µg/kg bw, respectively.

48. The LB and UB mean and 97.5th percentile chronic exposures were 0.044 – 0.049 µg/kg bw and 0.084 – 0.087 µg/kg bw for vegans, respectively. For vegetarians the LB and UB mean and 97.5th percentile exposures were 0.038 – 0.043 µg/kg bw and 0.078 – 0.092 µg/kg bw, respectively.

Ethnicity

49. Total acute and chronic exposures to EAs in women from different ethnic groups are presented in Table 5 and Table 6.

Table 5: Acute exposure to EAs in women of childbearing age by ethnicity

Ethnic group	Exposure LB-UB (µg/kg bw)	
	Mean	P97.5
Asian or Asian British (n=135)	0.057 – 0.068	0.11 – 0.13
Black or Black British (n=82)	0.047 – 0.055	0.10 – 0.11

White (n = 2234) 0.052 - 0.056 0.12 - 0.13

LB= lower bound; UB= upper bound.

Table 6: Chronic exposure to EAs in women of childbearing age by ethnicity

Ethnic group	Exposure LB-UB (µg/kg bw)	Exposure LB-UB (µg/kg bw)
	Mean	P97.5
Asian or Asian British (n=135)	0.034 - 0.046	0.071 - 0.097
Black or Black British (n=82)	0.027 - 0.033	0.073 - 0.085
White (n = 2234)	0.030 - 0.034	0.073 - 0.079

LB= lower bound; UB= upper bound.

Risk Characterisation

50. The available data suggested that EAs produce direct peripheral effects (uterotonic action or vasoconstriction), indirect peripheral effects (serotonin antagonism or adrenergic blockade), and central nervous system effects (induction of hypothermia and emesis or control of the secretion of pituitary hormones). Due to their structural similarities EAs have been suggested to act as agonists or antagonists to noradrenaline, dopamine and serotonin neurotransmitters.

51. Exposure to EAs has also been associate with pregnancy hindrance by interfering with eggs implantation and embryotoxicity in rodents, negative effects on maternal blood supply to the placenta in ewes and sirenomelia associate with in utero exposure in humans. EAs can also negatively affect lactation due to their hormone mimicking activity, in particular LH/FSH balance and prolactin (Della-Giustina eta al., 2005).

52. EFSA (2012) established an ARfD of 1 µg/kg bw and a TDI of 0.6 µg/kg bw per day for EAs. JECFA establish a group TDI for the sum of total EAs in the diet at the same value as the group ARfD of 0.4 µg/kg bw per day.

53. Mean and 97.5th percentile total acute estimated exposures were 0.052 to 0.057 and 0.12 to 0.13 µg/kg bw respectively, mean and 97.5th percentile total chronic estimated exposures were 0.031 to 0.035 and 0.072 to 0.080 µg/kg bw respectively. All estimated exposures are below the respective ARfD and TDI established by EFSA and are therefore not of toxicological concern. The estimated exposures are also below the HBGV established by JECFA.

54. The food groups contributing most to the overall exposures were wholemeal and granary bread, white sliced bread and other bread. However, it should be noted that the dietary exposure estimates are based on a limited number of food groups and that data from ready-to-eat foods analysis are scarce. A contribution to overall EAs exposure from other foods can therefore not be excluded.

55. 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. The relatively small data set and limited number of EAs evaluated further as a level of uncertainty to the results.

56. The lowest prescribed dose of ergotamine for acute migraine treatment is 13-26 µg ergotamine/kg bw, the maximum recommended oral therapeutic dose in adults for ergotamine over a period of 30 days (to avoid possible severe adverse effects such as peripheral vasoconstriction) is 8 µg/kg bw per day. EFSA concluded that 2 µg/kg b.w. ergometrine, used to induce uterine contraction, is likely to be close to a NOAEL and that the margin between this dose in a sensitive subpopulation and the group ARfD of 1 µg/kg bw is adequate. The estimate exposures here are below any therapeutical doses reported to have adverse effects.

Conclusions

57. Applying occurrence data from the 2011 TDS for EAs and consumption data for woman of childbearing age, all estimated mean and 97.5th percentile exposures are below the respective ARfD of 1 µg/kg bw and TDI of 0.6 µg/kg bw and are therefore not of toxicological concern. These exposures are also below the reported therapeutical doses of natural or synthetic EAs.

58. However, it should be noted that the assessment was based on a relatively small sample size (food groups, EAs tested) and that applying consumption data for woman of childbearing age may not be representative of the maternal diet.

Questions on which the views of Committee are sought

I. Do Members have any comments on the potential risk of consuming ergot alkaloids in the maternal diet?

II. Does the Committee have any further comments?

Secretariat

July 2022

Abbreviations

ACTH Adrenocorticotrophic hormone

ARfD Acute reference dose

BfR Bundesamt fuer Risikobewertung/German Federal Institute for Risk Assessment

BMDL Benchmark Dose Lower Confidence Limit

CNS Central nervous system

CONTAM Panel on Contaminants in the Food Chain

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

DM	Dry matter
DNA	Deoxyribonucleic acid
EAs	Ergot alkaloids
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FSH	Follicle-stimulating hormone
GI tract	Gastrointestinal tract
HBGV	Health based guidance value
IARC	International Agency for Research on Cancer
i.v.	Intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LA	Lysergic acid
LB	Lower bound
LC	Liquid chromatography

LH	Luteinizing hormone
LOAEL	Lowest observed adverse effect level
Misc	Miscellaneous
MS	Mass spectrometry
NDNS	National Diet & Nutrition Survey
ng/g	nanograms per gram
NOAEL	No observed adverse effect level
PRL	Prolactin
SACN	Scientific Advisory Committee on Nutrition
sc	Subcutaneous
SCE	Sister chromatid exchange
TDI	Tolerable daily intake
TDS	Total Diet Study
UB	Upper bound
UF	Uncertainty factor
WHO	World Health Organisation

µg	µg = microgram
µg/g	microgram per gram
µg/kg	microgram per kilogram
µg/L	microgram per litre

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Appendix A

Literature Search Terms for Ergot Alkaloids (January 2022 - June 2022)

acute toxicity

chronic toxicity

reproductive toxicity

biomarkers (exposure/ toxicity)

maternal health

preconception

conception

pregnancy

post-natal

lactation

fetus/ foetus/ fetal /foetal

placenta

pre-term

preeclampsia

cancer/ carcinogen(icity)

teratogen(icity)

absorption

distribution

metabolis

Appendix B

Food groups analysed in the TDS for EAs. The information can be found in Table 22 of the report and summarised below.

Table 5: List of all food groups analysed for ergot alkaloids (EAs).

Food groups	Category	Occurrence data total EAs (µg/kg)
Bread	White sliced bread	14.08
Bread	White unsliced bread	11.88
Bread	Brown bread	27.29
Bread	Wholemeal and granary bread	33.69
Bread	Other bread	23.29
Miscellaneous cereals	Flour	19.46
Miscellaneous cereals	Buns cakes and pastries	8.25

Miscellaneous cereals	Savoury biscuits	2.23
Miscellaneous cereals	Sweet biscuits	9.34
Miscellaneous cereals	Chocolate biscuits	4.90
Miscellaneous cereals	Breakfast cereals	3.07
Miscellaneous cereals	Rice	7.08
Miscellaneous cereals	Other cereal products	0.00
Miscellaneous cereals	Pasta	0.64
Miscellaneous cereals	Pizza	0.00
Miscellaneous cereals	Group sample	6.94
Non-alcoholic beverages	Branded food drinks	4.30
(With bottles water)	Alternatives to milk	0.00
Alcoholic drinks	Beer	0.00
Alcoholic drinks	Cider	0.00
Snacks	Other snacks (not potato based)	0.00
Sandwiches	Sandwiches	3.65

Sandwiches

Group sample

13.46