

First draft statement on the potential risks from ergot alkaloids in the maternal diet

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

3. The Committee discussed the potential risk from EAs in the maternal diet (TOX/2022/36) at the COT meeting in July 2021. At this meeting, the Committee noted that only a single study on sirenomelia associated with EAs was included in the discussion paper. Members therefore asked for additional animal studies to be added, if available, to provide supporting evidence. Further information was also requested on the extend of gastrointestinal absorption and the prolactin effect. The requested information has been included in the respective sections of the first draft statement.

4. The first draft statement on ergot alkaloids can be found in Annex A.

Questions for the Committee

The Committee are asked to consider the following question:

- a) Do the Committee have any comments on the structure or content of the draft Statement?
- b) Do the Committee have any comments on the additional information presented in this draft statement?
- c) Does the Committee have any other comments?

Secretariat

July 2023

Annex A to TOX/2023/39

Introduction

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Background

3. Ergot alkaloids (EA) are secondary metabolites produced by the fungi families Clavicipitaceae and Trichocomaceae, with *Claviceps purpurea* being the most widespread 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). While the -inine forms of EAs are considered biologically inactive, interconversion occurs under various conditions and hence EFSA included both forms of EAs (-ine and inine) in their assessment (EFSA, 2005, Tasker and Wipf, 2021). Bromocriptine is a synthetic ergoline derivative and is used in the treatment of Parkinson's disease and pituitary tumours (Herdman et al., 2001).

5. Most of the naturally occurring EAs show a tetracyclic ergoline ring system consisting of four fused rings in which position N6 carries a methyl group,

and there is a double bond at either C8,9 or at C9,10. Ergometrine is a simple derivative of lysergic acid. Other EAs considered in this evaluation are peptide alkaloids with a cyclized tripeptide as a substituent at C8. Different chemical structures are illustrated in Figure 1 (EFSA, 2012; JECFA, 2023).

Figure 1: Chemical structures of different EAs (JECFA, 2023).

Toxicity

6. Due to their structural similarities, EAs have been suggested as 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 in animals and humans suggested that EAs are absorbed from the gastrointestinal (GI) tract and subjected to oxidative biotransformation, likely involving cytochrome P450 3A4 (CYP3A4) via hydroxylation in the liver. The intestinal absorption of hydrogenated ergot peptide alkaloids generally ranged between 10 and 30 % (Eckert et al., 1978; Olver et al., 1980, Aellig et al., 1977; Little et al., 1982, Wyss et al., 1991). Although cytochrome P450 3A4 metabolizes EAs via hydroxylation, EAs have also been shown to bind to it as an inhibitor substrate. Recent studies showed that many EAs are derivatives of lysergic acid (LA) and that P450 monooxygenase and its cluster clavine oxidase (CloA) play a key role in its biosynthesis (Gerhards et al., 2014, Haarmann et al., 2006; Mulac and Humpf, 2011). Furthermore, cytochrome P450 3A4 is involved in the biosynthetic pathway of EAs in *Claviceps purpurea* (Haarmann et al., 2006).

8. No studies were available on the toxicokinetics of dietary EAs in humans. However, human data were available on ergotamine used as a pharmaceutical to treat Parkinson's disease. Absorption of ergotamine from the GI tract was poor after oral/sublingual administration and bioavailability was

further reduced by high pre-systemic hepatic metabolism. Ergotamine tartrate can also be given rectally, to improve absorption, yet bioavailability was 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

9. *In vivo* studies identified varying sensitivities to EAs in different animal species, with rabbits being the most sensitive with LD50 values between 0.9 and 3.2 mg/kg body weight (bw). The LD50s were determined by a series of experiments using naturally occurring and (semi-) synthetic EAs by intravenous (i.v.), subcutaneous (s.c.) and oral exposures (in 2 % gelatine) in mouse, rat and rabbit (Griffith et al., 1978, abstract only). All naturally occurring EAs demonstrated a low oral acute toxicity compared to i.v. administrations, suggesting low absorption and high pre-systemic metabolism via the oral route. Based on the LD50s (27.8 – 1200 mg/kg), EFSA concluded EAs overall to exhibit moderate oral acute toxicity (EFSA, 2012).

10. 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).

11. 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 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). 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. Additional symptoms of ergotism were lethargy or depression (Arroyo-Manzanares et al., 2017; EFSA, 2012).

12. Limited data were available for individual EAs and their toxic effects on humans. The available data mostly consisted of receptor interaction analysis for single substances in dopamine over-expressing cells or tumour cells. Studies indicated that ergocryptine, ergocristine, and bromocryptine produced an elevation in baseline dopamine release of approximately 400% with effective

concentrations of approximately 30 µM (Larson et al.,1995; 1999). No toxic effects were shown in the studies.

13. 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 (contraction and dilation of the pupils), muscular weakness, tremor and rigidity in mammals.

Chronic toxicity

14. A study by Valente et al. (2020) showed EAs to be structurally similar to biogenic amines, such as 5-hydroxytryptamine (serotonin), which allowed EAs to interact with serotonin receptors and act as agonists or antagonists when consumed by steers. In contrast, a study by Kalkman et al. (1982) showed vasoconstriction based on adrenergic-like receptors in rats injected intravenously with ergometrine.

15. A study by Korn et al. (2014) reported spontaneous alopecia, erosions, crusts and necrosis, specifically of the tail area in a rabbit colony, exclusively in young rabbits aged 113 ± 20 days (14 out of 103 rabbits) fed with hay and a commercial pelleted feed. The results of the study indicated that EAs may have been the cause of the tail necrosis. Immunoassays on blood samples showed a mean and maximum EAs concentration of 410 µg/kg and 1,700 µg/kg, respectively. In addition, EAs were detected in the faeces of the affected rabbits at levels up to 200 µg/kg. The mean and maximum dietary intakes of total EAs were 17 and 71 µg/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.

16. 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, abstract only). The NOAELs were 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).

17. 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.

18. To minimize toxicity and avoid adverse effects such as nausea, vomiting, weakness, muscle pains, paraesthesiae and coldness of the extremities from acute migraine treatment with ergotamine, the dosage was 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 case reports 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).

Genotoxicity and Carcinogenicity

19. No genotoxicity or mutagenic effects were demonstrated for ergotamine tartrate (Et) in the *Salmonella typhimurium* (St) assay (10-10,000 µg/plate for 48 hours) and mouse lymphoma TK+/- assay (7.7-108 µg/mL for 4h) (Seifried et al., 2006). An *in vitro* study by Roberts and Rand (1977) indicated that ergotamine induced chromosomal abnormalities in human lymphocytes and leukocytes. In a 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.

20. However, due to limited and contradictory data on the genotoxic and mutagenic effects of EAs, EFSA (2012) considered the available genotoxicity studies to be insufficient, except for ergotamine, concluding that the available data on ergotamine did not indicate bacterial or mammalian cell mutation.

21. EAs are not considered carcinogenic and have not been assessed by the International Agency for Research on Cancer (IARC). However, they have been suggested to be 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 Lehmyer, 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. It was noted that further information is required to confirm the cytotoxic effect pathway, but preliminary results suggested 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).

Reproductive and Developmental toxicity

22. Several studies reported adverse 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; Fayrer-Hosken et al., 2013; Klotz et al., 2019). These adverse effects on the reproductive process in rodents have generally been observed at higher doses than the lowest-observed-adverse-effect levels (LOAELs) in repeat dose studies (EFSA, 2012). Studies in livestock also reported reduced reproductive performance, particularly in female cattle, after EAs exposure. 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 (Poole and Poole, 2019).

23. 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 EAs at a concentration of 0.8 ug of ergovaline/g diet during gestation. Results demonstrated that exposure to EAs during mid and/or late gestation in ewes reduced fetal growth. A more recent study in ewes 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 (Klotz et al., 2019). *In utero* exposure to EAs in pregnant ewes, especially during phase two of gestation was seen to alter fetal growth, muscle fibre formation, and miRNA expression (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 was 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).

24. 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, abstract only available). 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 and the inhibition of prolactin has been seen in humans, laboratory animals, and livestock animals (Arroyo-Manzanares et al., 2017; Prendiville et al., 2000). Intraperitoneal injection of 1 mg ergocornine methane sulfonate in lactating rats temporarily inhibited milk production, the effect being prevented by treatment with prolactin (Zeilmakla and Carlsen, 1962). The potency of EAs to inhibit prolactin secretion in rats decreased in the following order: ergocornine > ergocryptine > dihydro-ergocryptine > dihydro-ergocornine > ergotamine > ergometrine (Griffith et al., 1978, abstract only). Decreases in prolactin levels were observed in rats of both sexes with increasing amount of α -ergocryptine in the diet (Janssen et al., 2000). Shaar and Clemens (1972) suggested that EAs directly affect the pituitary therefore preventing prolactin secretion, resulting in partial inhibition of lactation.

25. A single case study suggested that exposure to methylergonovine maleate (EA derivate) at a critical stage of organogenesis could result in the development 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 (Cozzolino et al., 2016).

26. 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).

27. One epidemiological study linked the use of purified ergotamine to congenital abnormalities during pregnancy in humans. Ergotamine was used to treat acute 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 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).

Health-based guidance values

28. EFSA (2012) considered the vasoconstrictive effect as the critical effect for EAs and derived a BMDL10 of 0.33 mg/kg bw per day, based on the finding of tail muscular atrophy in rats fed for 13 weeks with ergotamine. EFSA applied an overall uncertainty factor (UF) of 300, the default UF of 100 for intra- and interspecies differences and an additional UF of 3 to account for deficiencies in the database, to derive 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 to the derivation of the tolerable daily intake (TDI) for the extrapolation from a sub-chronic to a chronic study. 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.

29. 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 lowest observed effect level (LOEL) to a no-observed effect level (NOEL) and an UF of 3.16 to account for possible interindividual toxicodynamic differences. Applying a composite UF of 6.3 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 EAs exposure

30. 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, a limit of 100 µg EAs/kg applies, which will be 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 reflected in a higher maximum level. Milled rye products are subject to an EAs limit of 500 µg/kg, which will be 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.

31. EFSA estimated chronic dietary exposure in the adult population between 0.007 and 0.08 µg/kg 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).

32. 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).

33. Caraballo et al. (2019) reported concentrations of up to 47 µg/kg in grains and grain-based composites. In cereal and flour, particularly rye, EAs concentrations of over 7 mg/kg have been reported (Krska and Crews, 2008). 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. Storm et al. (2011) detected EAs in Danish rye flour samples 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) detected EAs in 83 % of the tested rye grain, 94 % of rye flour, and 100 % of rye bran and flake samples. Ergocryptine, ergocristine, and ergotamine were the most common EAs detected in the majority of surveys and foods sampled. 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

34. Estimated exposures 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).

35. The total diet study (TDS) data (Stratton et al., 2017) was based on 28 food groups which were further divided to produce 138 food categories. Total EAs and the epimers were determined by LC/MS/MS (Carbonell-Rozas et al., 2021) of which ergocristine, ergotamine, ergocornine, ergosine, ergocryptine, ergometrine, ergocristinine, ergotaminine, ergocorninine, ergosinine, ergocryptinine and ergometrinine were the most frequent forms detected. More data on each specific subset are available in the TDS study report (Diet Study (TDS) – Mycotoxin Analysis Report, 2017).

36. 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 1 (acute) and Table 2 (chronic).

Table 1: Acute exposure to ergot alkaloids in women of childbearing age; food groups not containing EAs have been removed.

Food groups	Exposure (ng/kg bw)	
	LB - UB, Mean	Exposure (ng/kg bw) LB - UB, P97.5
White sliced bread	9.2-9.3	41.0
White unsliced bread	6.0-6.1	34.0-35.0
Brown bread	2.3	33.0
Wholemeal and granary bread	24.0	91.0
Other bread	15.0	68.0
Misc cereals FLOUR	1.5-1.7	12.0-13.0

Misc cereals Buns cakes and pastries	1.9-2.7	9.4-13.0
Misc cereals Savoury biscuits	0.9	7.6-7.7
Misc cereals Sweet biscuits	1.5-1.6	8.4-9.0
Misc cereals Chocolate biscuits	0.6	5.4-5.8
Misc cereals Breakfast cereals	3.0	18.3-18.4
Misc cereals RICE	0-6.2	0-25.0
Misc cereals Other cereal products	1.0-1.7	8.8-15.0
Misc cereals PASTA	2.2-6.5	8.9-27.0
Misc cereals Pizza	7.2-7.5	54.0-56.0
Total	52.0-57.0	120.0-130.0

LB= lower bound; UB= upper bound.

Table 2: Chronic exposure to ergot alkaloids in women of childbearing age; food groups not containing EAs have been removed.

Food groups	Exposure (ng/kg bw) LB - UB, Mean	Exposure (ng/ng bw) LB - UB, P97.5th percentile
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White sliced bread	4.0-4.1	21.4-21.5
White unsliced bread	2.1	12.8-12.9
Brown bread	0.8	10.0
Wholemeal and granary bread	0.011	52.0
Other bread	0.0055	29.0
Misc cereals FLOUR	0.6	4.7-5.2
Misc cereals Buns cakes and pastries	0.7-0.9	3.8-5.2
Misc cereals Savoury biscuits	0.3	3.1
Misc cereals Sweet biscuits	0.6	3.6-3.9
Misc cereals Chocolate biscuits	0.2	1.8-1.9
Misc cereals Breakfast cereals	1.9	8.9-9.0
Misc cereals RICE	0-2.4	0-12
Misc cereals Other cereal products	0.3-0.5	2.8-4.8

Misc cereals PASTA	0.7-2.1	3.5-10.0
Misc cereals Pizza	1.9-2.0	15.0
Total	31.0-35.0	72.0-80.0

LB= lower bound; UB= upper bound

Exposures in subpopulation groups

Vegans and Vegetarians

37. The number of vegans (n=10) and vegetarians (n=112) among the total number of consumers (n= 2556) were relatively small.

38. The LB and UB mean and 97.5th percentile acute exposures were 64.0 – 70.0 ng/kg bw and 127.0 – 130.0 ng/kg bw for vegans, respectively. For vegetarians the LB and UB mean and 97.5th percentile exposures were 61.0 – 67.0 ng/kg bw and 135.0 – 140.0 ng/kg bw, respectively.

39. The LB and UB mean and 97.5th percentile chronic exposures were 44.0– 49.0 ng/kg bw and 84.0 – 87.0 ng/kg bw for vegans, respectively. For vegetarians the LB and UB mean and 97.5th percentile exposures were 38.0 – 43.0 ng/kg bw and 78.0 – 92.0 ng/kg bw, respectively.

Ethnicity

40. The number of Asian or Asian British women of childbearing age (n=135) and Black or Black British women of childbearing age (n=82) were relatively small compared to White women of childbearing age (n=2234).

41. The LB and UB mean and 97.5th percentile acute exposures were 57.8- 68.0 ng/kg bw and 110 – 130.0 ng/kg bw for Asian women, respectively. The LB and UB mean and 97.5th percentile acute exposures were 47.0-55.0 ng/kg bw and 100 – 110.0 ng/kg bw for Black women, respectively. For White women the LB and UB mean and 97.5th percentile exposures were 52.0-56.0 ng/kg bw and 120.0 – 130.0 ng/kg bw, respectively.

42. The LB and UB mean and 97.5th percentile chronic exposures were 34.0-46.0 ng/kg bw and 71.0-97.0 ng/kg bw for Asian women, respectively. The LB and UB mean and 97.5th percentile acute exposures were 27.0-33.0 ng/kg bw and 73.0-85.0 ng/kg bw for Black women, respectively. For White women the LB and UB mean and 97.5th percentile exposures were 30.0-34.0 ng/kg bw and 73.0-79.0 ng/kg bw, respectively.

Risk Characterisation

43. 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.

44. Exposure to EAs has also been associated with pregnancy hindrance by interfering with egg implantation and embryotoxicity in rodents, negative effects on maternal blood supply to the placenta in ewes and sirenomelia associated 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 et al., 2005).

45. EFSA (2012) established an ARfD of 1 µg/kg bw and a TDI of 0.6 µg/kg bw per day for EAs. JEFCA 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.

46. Using TDS mycotoxin data, mean and 97.5th percentile total acute estimated exposures were 52.0 to 57.0 and 120.0 to 130.0 ng/kg bw respectively, mean and 97.5th percentile total chronic estimated exposures were 31.0 to 35.0 and 72.0 to 80.0 ng/kg bw respectively. All estimated exposures are below the respective ARfD and TDI and are therefore not of toxicological concern. The estimated exposures are also below the HBGV established by JECFA.

47. While not showing convincing evidence of pharmacological activity, the lowest prescribed dose of ergotamine for treatment of migraine was 13-26 µg ergotamine/kg bw, the maximum recommended oral therapeutic dose in adults for ergotamine over a period of 30 days was 8 µg/kg bw per day, to avoid possible severe adverse effects such as peripheral vasoconstriction (EFSA, 2012). 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 sufficiently protective. The estimate exposures based on the TDS data were below any therapeutical doses reported to have adverse effects.

48. 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.

49. 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 add a level of uncertainty to the results.

Conclusions

50. Applying occurrence data from the 2011 TDS for EAs and consumption data from the NDNS 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 minimum effective doses used therapeutically or any therapeutic dose reported to have adverse effects of natural or synthetic EAs.

51. 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.

COT

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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

References

Aellig WH, Nüesch E (1977). Comparative pharmacokinetic investigations with tritium-labeled ergot alkaloids after oral and intravenous administration man. Int J Clin Pharmacol Biopharm. 15(3):106-12. PMID: 403149. DOI:

<https://pubmed.ncbi.nlm.nih.gov/403149/>

Arroyo-Manzanares N., Gámiz-Gracia L., García-Campaña A.M., Di Mavungu J.D, De Saeger S. (2017). Ergot Alkaloids: Chemistry, Biosynthesis, Bioactivity, and Methods of Analysis. Fungal Metabolites 887-929. DOI [10.1007/978-3-319-25001-4_1](https://doi.org/10.1007/978-3-319-25001-4_1)

Bernard N, Jantzen H, Becker M, Pecriaux C, Bénard-Larivière A, Montastruc JL, Descotes J, Vial T (2015). Severe adverse effects of bromocriptine in lactation inhibition: a pharmacovigilance survey. Royal College of Obstetricians and Gynaecologists, 122(9): 1244-51. DOI <https://doi.org/10.1111/1471-0528.13352>

Bogun N, Mathies R, Baesecke J (2011). Angiospastic occlusion of the superficial femoral artery by chronic ergotamine intake. Deutsche Medizinische Wochenschrift, 136(1-2): 23-6. DOI <https://doi.org/10.1055/s-0030-1269435>

Bryła M, Szymczyk K, Jędrzejczak R, Roszko M (2015). Application of liquid chromatography/ ion trap mass spectrometry technique to determine ergot alkaloids in grain products. Food Technol Biotechnol 53:18-28. DOI <https://doi.org/10.17113/ftb.53.01.15.3770>

Britt JL, Greene MA, Bridges Jr WC, Klotz JL, Aiken GE, Andrae JG, Pratt SL, Long NM, Schrick FN, Strickland JR, Wilbanks SA, Miller Jr MF, Koch BM, Duckett SK (2019). Ergot alkaloid exposure during gestation alters. I. Maternal characteristics and placental development of pregnant ewes. Journal of Animal Science, 97(4):1874-90. DOI <https://doi.org/10.1093%2Fjas%2Fskz068>

Caraballo D, Toloso J, Ferrer E, Berrada H (2019). Dietary exposure assessment to mycotoxins through total diet studies. A review. Food and Chemical Toxicology, 128: 8-20. DOI <https://doi.org/10.1016/j.fct.2019.03.033>

Carlsen RA, Zeilmaker GH, Shelesnyak MC. (1961). Termination of early (pre-nidation) pregnancy in the mouse by single injection of ergocornine methanesulfonate. J Reprod Fertil. 2:369-73. DOI: <https://doi.org/10.1530/jrf.0.0020369>

Cassady JM, Li GS, Spitzner EB, Floss H, Clemens JA (1974). Ergot alkaloids. Ergolines and related compounds as inhibitors of prolactin release. J Med Chem. (3):300-7. DOI <https://doi.org/10.1021/jm00249a009>

Chestnut D.H. Chronic Pain during and after Pregnancy (2020). Chestnut's Obstetric Anesthesia. DOI Book.

Cozzolino M, Riviello C, Fichtel G, Di Tommaso M (2016). Brief Report Exposure to Methylergonovine Maleate as a Cause of Sirenomelia. Birth Defects Research Part A: Clinical and Molecular Teratology, 106(7): 643-7. DOI <https://doi.org/10.1002/bdra.23503>

COT (2017). Review of potential risks from mycotoxins in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. Available: [tox2017-30_0.pdf \(food.gov.uk\)](#).

Crews C, Anderson WAC, Rees G, Krska R (2009). Ergot alkaloids in some rye-based UK cereal products. Food Addit Contam Part B Surveill 2:79–85.

DOI <https://doi.org/10.1080/02652030903042509>

Czeizel A (1989). Teratogenicity of ergotamine J Med Genet 26(1):69-70 DOI <http://dx.doi.org/10.1136/jmg.26.1.69-a>

Della-Giustina K and Chow G (2003). Medications in pregnancy and lactation. Emergency Medicine Clinics of North America, 21(3): 585-613. DOI [https://doi.org/10.1016/s0733-8627\(03\)00037-3](https://doi.org/10.1016/s0733-8627(03)00037-3)

De Ruyck K, De Boevre M, Huybrechts I, De Saeger S (2015). Dietary mycotoxins, co-exposure, and carcinogenesis in humans: Short review. Mutation Research/Reviews in Mutation Research, 766: 32-41. DOI <https://doi.org/10.1016/j.mrrev.2015.07.003>

Duckett SK, Andrae JG, Prat SL (2014). Exposure to Ergot alkaloids during gestation reduces fetal growth in sheep. Frontiers in Chemistry, 21: 2:68. DOI <https://doi.org/10.3389/fchem.2014.00068>

Dighe, R., Vaidya, V.G., (1988). Induction of sister chromatid exchanges by ergot compounds in Chinese hamster ovary cells in vitro. Teratog. Carcinog. Mutagen. 8, 169–174.

DOI <https://doi.org/10.1002/tcm.1770080306>

Duesterhoeft S.M., Ernst L.M., Siebert J.R., Kapur RK (2007). Five cases of caudal regression with an aberrant abdominal umbilical artery: Further support for a caudal regression-sirenomelia spectrum. Am J Med Genet A. 15;143A(24):3175-84. DOI [10.1002/ajmg.a.32028](https://doi.org/10.1002/ajmg.a.32028)

Dusemund B, Altmann H-J and Lampen A, (2006). II. Toxikologische Bewertung Mutterkornalkaloidkontaminierter Roggenmehle. Journal of Consumer Protection and Food Safety, 1, 150-152. DOI <https://link.springer.com/article/10.1007/s00003-006-0025-2>

Eckert, H., Kiechel, J.R., Rosenthaler, J., Schmidt, R., Schreier, E. (1978). Biopharmaceutical Aspects. In: Berde, B., Schild, H.O. (eds) Ergot Alkaloids and

Related Compounds. Handbook of Experimental Pharmacology / Handbuch der experimentellen Pharmakologie, vol 49. Springer, Berlin, Heidelberg. DOI: [10.1007/978-3-642-66775-6_11](https://doi.org/10.1007/978-3-642-66775-6_11)

EFSA (2012). Scientific Opinion on Ergot alkaloids in food and feed. EFSA Journal, 10(7): 2798. Available: [Ergot alkaloids in food and feed | EFSA \(europa.eu\)](https://efsa.europa.eu/en/efsa-journal/scientific-opinion-on-ergot-alkaloids-in-food-and-feed).

Commission Regulation (EU) 2021/1399 of 24 August 2021 amending Regulation (EC) No 1881/2006 as regards maximum levels of ergot sclerotia and ergot alkaloids in certain foodstuffs (Text with EEA relevance). Available: [EUR-Lex - 32021R1399 - EN - EUR-Lex \(europa.eu\)](https://eur-lex.europa.eu/eli/reg/2021/1399/oj).

Fitzgerald P and Dinan TG (2008). Prolactin and dopamine: what is the connection? A review article. Journal of Psychopharmacology, 22(2 Suppl), 12-9. DOI <https://doi.org/10.1177/0269216307087148>

Fayrer-Hosken R.A., Hill N.S., Heusner G.L., Traylor-Wiggins W., Turner K (2013). The effects of ergot alkaloids on the breeding stallion reproductive system. Equine Vet J Suppl 12 (45):44-7. DOI <https://doi.org/10.1111/evj.12164>

Fröhlich G, Kaplan V, Amann-Vesti B (2010). Holy fire in an HIV-positive man: a case of 21st century ergotism. Canadian Medical Association Journal, 182 (4): 378-80. DOI <https://doi.org/10.1503/cmaj.091362>

FSA (2014). Monitoring the Presence of Ergot Alkaloids in Cereals and a Study of a Possible Relationship between Occurrence of Sclerotia Content and Levels of Ergot Alkaloids. Available: [Monitoring the presence of ergot alkaloids in cereals | Food Standards Agency](https://www.fda.gov/food/monitoring-presence-ergot-alkaloids-cereals).

Garcia GD, Goff Jr JM, Hadro NC, I-Donnell SD, Grestorex PS (2000). Chronic ergot toxicity: A rare cause of lower extremity ischemia. Journal of Vascular Surgery, 31(6): 1245-7. DOI <https://doi.org/10.1067/mva.2000.105668>

Gerhards N, Neubauer L, Tudzynski P, Li SM (2014). Biosynthetic Pathways of Ergot Alkaloids. Toxins, 6(12):3281-95. DOI <https://doi.org/10.3390/toxins6123281>

Greene MA, Britt JL, Powell RP, Feltus FA, Bridges WC, Bruce T, Klotz JL, Miller MF, Duckett SK (2019). Ergot alkaloid exposure during gestation alters: 3. Fetal growth, muscle fiber development, and miRNA transcriptome. Journal of Animal Science, 97(7):3153-68. DOI <https://doi.org/10.1093/jas/skz153>

Graf WD and Shepard TH (1997). Uterine contraction in the development of Möbius syndrome. *Journal of Child Neurology*, 12(3): 225-7. DOI <https://doi.org/10.1177/088307389701200315>

Griffith, R.W., Grauwiler, J., Hodel, Ch., Leist, K.H., Matter, B., 1978. In: Berde, B., Schild, H.O. (Eds.), *Toxicologic Considerations. Ergot Alkaloids and Related Compounds*. Springer Verlag, Berlin, Heidelberg, New York, pp. 805–851, abstract only. DOI <https://rd.springer.com/book/10.1007/978-3-642-66775-6>

Guggisberg H (1954). Changes in the therapeutic use of ergot. *Ther Umsch*. 11(4):77-9. DOI na.

Haarmann T, Ortel I, Tudzynski P, Keller U (2006). Identification of the cytochrome P450 monooxygenase that bridges the clavine and ergoline alkaloid pathways. *ChemBioChem – Chemistry Europe*. 7(4):645-52. DOI <https://doi.org/10.1002/cbic.200500487>

Janssen GB, Beems RB, Elvers LH, Speijers GJ (2000b). Subacute toxicity of α -ergocryptine in Sprague-Dawley rats. 2: metabolic and hormonal changes. *Food Chem Toxicol*. 38:689–95. DOI: [https://doi.org/10.1016/S0278-6915\(00\)00055-7](https://doi.org/10.1016/S0278-6915(00)00055-7)

JECFA (2021). Safety evaluation of certain food additives and contaminants. Summary report of the ninety-first meeting. Available: [Ninety-first meeting - Joint FAO/WHO Expert Committee of Food Additives \(JECFA\)](#).

JECFA (2023). Safety evaluation of certain contaminants in food: prepared by the ninety-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Available: [Safety evaluation of certain contaminants in food: prepared by the ninety-first meeting of the Joint FAO/WHO Expert Committee on Food Additives \(JECFA\)](#).

Jolivet A., Robyn C., Huraux-Rendu C., Gautray J.P. (1978). Effect of ergot alkaloid derivatives on milk secretion in the immediate postpartum period. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 7(1):129-134. DOI clinical trial.

Kalkman, H.O.; Van Gelderen, E.M.; Timmermans, P.B.; Van Zwieten, P.A. (1982) Involvement of α 1- and α 2-adrenoceptors in the vasoconstriction caused by ergometrine. *Eur. J. Pharmacol*. 78, 107–111.

DOI [https://doi.org/10.1016/0014-2999\(82\)90377-6](https://doi.org/10.1016/0014-2999(82)90377-6)

- Klotz J. (2015). Activities and Effects of Ergot Alkaloids on Livestock Physiology and Production. *Toxins (Basel)* 7(8), 2801-2821. DOI <https://doi.org/10.3390/toxins7082801>
- Klotz JL, Britt JL, Miller MF, Snider MA, Aiken GE, Long NM, Pratt SL, Andrae GJ, Duckett SK (2019). Ergot alkaloid exposure during gestation alters: II. Uterine and umbilical artery vasoactivity. *Journal of Animal Science*, 97(4): 1891-1902. DOI <https://doi.org/10.1093/jas/skz069>
- Korn AK, Gross M, Usleber E, Thom N, Köhler K, Erhardt G (2014). Dietary ergot alkaloids as a possible cause of tail necrosis in rabbits. *Mycotoxin Residues*, 30(4):241-50. DOI <https://doi.org/10.1007%2Fs12550-014-0208-0>
- Krska R and Crews C (2008). Significance, chemistry and determination of ergot alkaloids: a review. *Food Additives and Contaminants: Part A, chemistry, analysis, control, exposure and risk assessment*, 25(6):722-31. DOI <https://doi.org/10.1080/02652030701765756>
- Larson, B.T., Harmon, D.L., Piper, E.L., Griffis, L.M., Bush, L.P. (1999). Alkaloid binding and activation of D2 dopamine receptors in cell culture. *J. Anim. Sci.* 77, 942-947. DOI <https://doi.org/10.2527/1999.774942x>
- Larson, B.T., Samford, M.D., Camden, J.M., Piper, E.L., Kerley, M.S., Paterson, J.A., Turner, J.T., (1995). Ergovaline binding and activation of D2 dopamine receptors in GH4ZR7 cells. *J. Anim. Sci.* 73, 1396-1400. DOI <https://doi.org/10.2527/1995.7351396x>
- Liabsuetrakul T., Choobun T., Peeyananjarassri K., Monir Islam Q. (2018). Prophylactic use of ergot alkaloids in the third stage of labour. *Cochrane Database Syst Rev* 7;6(6):CD005456. DOI <https://doi.org/10.1002/14651858.CD005456.pub3>
- Lieberman AN and Goldstein M (1985). Bromocriptine in Parkinson disease. *Pharmacological Review*. 37(2) 217-27. [Bromocriptine in Parkinson disease - PubMed \(nih.gov\)](https://pubmed.ncbi.nlm.nih.gov/281111/) (No DOI available)
- MacLeod RM and Lehmeyer J (1973). Suppression of Pituitary Tumor Growth and Function by Ergot Alkaloids. *Cancer Research* 33, 849-855, DOI not available.
- Mrusek M et al (2015). Identification of cellular and molecular factors determining the response of cancer cells to six ergot alkaloids. *Invest New Drugs*. 33(1):32-44. DOI <https://doi.org/10.1007/s10637-014-0168-4>

- Mulac D and Humpf HU (2011). Cytotoxicity and accumulation of ergot alkaloids in human primary cells. *Toxicology*, 282(3):112-21. DOI <https://doi.org/10.1016/j.tox.2011.01.019>
- Müller C, Kemmlein S, Klaffke H, Krauthause W, Preiss-Weigert A, Wittkowski R (2009). A basic tool for risk assessment: a new method for the analysis of ergot alkaloids in rye and selected rye products. *Mol Nutr Food Res* 53:500-507 DOI. <https://doi.org/10.1002/mnfr.200800091>
- Kjeldgaard Pedersen L, Rikke Damkjær Maimburg R, Hertz JM, Gjørup H, Klit Pedersen T, Møller-Madsen B, Rosendahl Østergaard J (2017). Moebius sequence – a multidisciplinary clinical approach. *Orphanet Journal of Rare Diseases*, 12(1):4. DOI: <https://doi.org/10.1186/s13023-016-0559-z>
- Little PJ, Jennings GL, Skews H, Bobik A (1982). Bioavailability of dihydroergotamine in man. *Br J Clin Pharmacol*, 13(6):785-90. DOI: [10.1111/j.1365-2125.1982.tb01866.x](https://doi.org/10.1111/j.1365-2125.1982.tb01866.x).
- Olver IN, Jennings GL, Bobik A, Esler M (1980). Low bioavailability as a cause of apparent failure of dihydroergotamine in orthostatic hypotension. *British Medical Journal*. 281(6235):275-276. DOI: [10.1136/bmj.281.6235.275-a](https://doi.org/10.1136/bmj.281.6235.275-a).
- Orton DA and Richardson RJ (1982). Ergotamine absorption and toxicity. *Postgraduate Medical Journal*, 58(675): 6-11. DOI: <https://doi.org/10.1136%2Fpgmj.58.675.6>
- Page R, Lester T, Rorie R, Rosenkrans Jr C (2019). Ergot Alkaloid Effects on Bovine Sperm Motility In Vitro. *Advance in Reproductive Science*, 7(1): 7-15. DOI: <https://doi.org/10.4236/arsci.2019.71002>
- Poole R and Poole DH (2019). Impact of Ergot Alkaloids on Female Reproduction in Domestic Livestock Species. *Toxins*, 11(6): 364. DOI <https://doi.org/10.3390/toxins11060364>
- Prendiville WJ, Elbourne D, McDonaals S (2000). Active versus expectant management in the third stage of labor. *Cochrane Database Systematic Reviews*, 3. DOI <https://doi.org/10.1002/14651858.cd000007>
- Perrin VL (1985). Clinical pharmacokinetics of ergotamine in migraine and cluster headache. *Clinical Pharmacokinetics* 10(4): 334-52. DOI <https://doi.org/10.2165/00003088-198510040-00004>

Reinhold L, Reinhardt K (2011). Mycotoxins in foods in Lower Saxony (Germany): results of official control analyses performed in 2009. *Mycotoxin Res* 27:137–143. DOI <https://link.springer.com/article/10.1007/s12550-011-0086-7>

Roberts G and Rand MJ (1977). Chromosomal damage induced by some ergot derivatives in vitro. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis* 48 (2):205-214. DOI [https://doi.org/10.1016/0027-5107\(77\)90162-2](https://doi.org/10.1016/0027-5107(77)90162-2)

Carbonell-Rozas L, Gamiz-Gracia L, Lara FJ, Garcia-Campana AM (2021). Determination of the main ergot alkaloids and their epimers in oat-based functional foods by ultra-high performance liquid chromatography tandem mass spectrometry. *Molecules*, 26(12): 3717. DOI <https://doi.org/10.3390/molecules26123717>

Seifried, H.E., Seifried, R.M., Clarke, J.J., Junghans, T.B., San, R.H.C. (2006). A compilation of two decades of mutagenicity test results with the Ames Salmonella typhimurium and L5178Y mouse lymphoma cell mutation assays. *Chem. Res. Toxicol.* 19, 627–644. DOI <https://doi.org/10.1021/tx0503552>

Shaar CJ, Clemens JA (1972). Inhibition of lactation and prolactin secretion in rats by ergot alkaloid. *Endocrinology*. 90:285–88 [abstract only]. DOI: <https://doi.org/10.1210/endo-90-1-285>

Silberstein SD and McCrory DC (2003). Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. *Headache*, 43(2): 144-66. DOI <https://doi.org/10.1046/j.1526-4610.2003.03034.x>

Smets K, Zecic A, Willems J (2004). Ergotamine as a possible cause of Möbius sequence: additional clinical observation. *Journal of Child Neurology*, 19(5): 398. DOI <https://doi.org/10.1177/088307380401900518>

Storm ID, Have Rasmussen P, Strobel BW, Hansen HCB (2008). Ergot alkaloids in rye flour determined by solid-phase cation-exchange and high-pressure liquid chromatography with fluorescence detection. *Food Addit Contam* 25:338–346. DOI <https://doi.org/10.1080/02652030701551792>

Stratton J, Anderson S, Leon I, Hepworth P, Chapman S, Christy J, Jardine S, Philips D, Setter R, Clough J, MacDonalds S (2017). Diet Study (TDS) – Mycotoxin Analysis. Final Report, FS102081. Fera Science Ltd, York (UK). Available: [Diet Study \(TDS\) – Mycotoxin Analysis Report, 2017 - Search \(bing.com\)](#)

Tasker NR and Wipf P (2021). Biosynthesis, total synthesis, and biological profiles of Ergot alkaloids. *Alkaloids Chemical Biology*, 85:1-112.

DOI <https://doi.org/10.1016/bs.alkal.2020.08.001>

Tfelt-Hansen, P., Saxena, P.R., Dahlof, C., Pascual, J., Lainez, M., Henry, P., Diener, H., Schoenen, J., Ferrari, M.D., Goadsby, P.J., (2000). Ergotamine in the acute treatment of migraine: a review and European consensus. *Brain* 123 (Pt 1), 9–18. DOI [10.1093/brain/123.1.9](https://doi.org/10.1093/brain/123.1.9)

Valente Eel, Klotz JL, Ahn G, McLeod KR, Herzing HM, King M, Harmon DL (2020) Ergot alkaloids reduce circulating serotonin in the bovine. *Journal of Animal Science*, 98(12).

DOI <http://dx.doi.org/10.1093/jas/skaa362>

Wyss, P.A., Rosenthaler, J., Nüesch, E., Aellig, W.H (1991). Pharmacokinetic investigation of oral and IV dihydroergotamine in healthy subjects. *Eur J Clin Pharmacol* 41, 597–602.

DOI: <https://doi.org/10.1007/BF00314992>

Appendix A

Food groups analysed in the TDS for EAs.

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)	3.65
Sandwiches	Sandwiches	13.46
Sandwiches	Group sample	n/a