Annex A to TOX/2026/11

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Introduction and Background

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Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) last considered the maternal diet and nutrition in relation to offspring health in its reports on 'The influence of maternal, foetal and child nutrition on the development of chronic disease in later life' (SACN, 2011) and on 'Feeding in the first year of life' (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health, focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery. Further information on the scope of the maternal health projects can be found in the Scope of the Nutrition and Maternal health project Annex.

2. SACN agreed that, where appropriate, other expert committees would be consulted and asked to complete relevant risk assessments. A provisional list of chemicals was proposed by SACN Members. However, this was subject to change following discussion by the COT. A scoping paper was presented to the Committee (TOX/2020/45) to define the scope of the work from a toxicological safety perspective and request their input on the selection of candidate chemicals or chemical classes that could be added or removed.

3. As part of this work, the Committee decided it would be useful to consider the use of dietary supplements during pregnancy. A scoping paper (TOX/2020/51) was presented, reviewing the dietary supplements commonly used during pregnancy. These supplements are not officially recommended by relevant health and regulatory authorities but are promoted by anecdotal evidence and unofficial sources as having various purported benefits.

4. The review, presented in the scoping paper, was confined to herbal dietary supplements which would be regulated under food law, as opposed to traditional herbal medicines, which are overseen by the Medicines and Healthcare Products Regulatory Agency (MHRA). Following this review, the COT suggested that *Echinacea* required further investigation, noting that both human and animal *in vitro* and **in vivo** data were available. The main areas of concern included general toxicity to the mother, effects on the development of the foetus or embryo and possible interactions with drugs.

5. Based on the COT's recommendations, a more extensive literature search was undertaken to evaluate the safety of Echinacea use during pregnancy, and the results are presented below (for full details of the search method, see Appendix A).

Background

Uses

6. *Echinacea* is a genus of herbaceous flowering plants, comprised of ten species and originally native to North America (Ahmadi et al., 2024). Three *Echinacea* species (*Echinacea purpurea, Echinacea pallida, and Echinacea angustifolia*) are used medicinally for the prevention and treatment of the common cold, influenza, and upper respiratory tract infections (Ardjomand-Woelkart and Bauer, 2015). *E. purpurea* is the most widely used and extensively studied of the three. Prior to 1968, *Echinacea angustifolia* and *Echinacea pallida* were considered to be different varieties of the same species until a revision of the genus described them as two separate species (WHO, 1999).

7. *Echinacea* herbal products are often sold as dietary supplements to enhance the immune function and to reduce the symptoms and duration of common cold and upper respiratory tract infections. These are popular products in North America and Europe, generating more than 300 million USD annually in the U.S. alone (Ahmadi et al., 2024).

8. *Echinacea* extracts are used for a broad range of ailments including respiratory infections (colds and flu, bronchitis, strep throat, toothache), urinary tract infections, skin disorders (Staphylococcus infections, cold sores, ulcers, wounds, burns, insect bites, eczema, allergies) and rheumatoid arthritis (Hudson, 2012). Between 0.5% (Heitmann et al., 2016) and 9.2% (Cuzzolin et al., 2010) of pregnant women report using *Echinacea* during pregnancy for the treatment of cold and flu, stimulating the immune system and the prevention of common cold (Cuzzolin et al., 2010; Holst et al., 2011).

Constituents and preparations

9. The fresh or dried aerial parts and the fresh pressed juice from the flowering tops of *E. purpurea*, as well as the whole plant, and the dried roots of *E. purpurea*, *E. pallida* and *E. angustifolia* are used medicinally. Different methods of extraction are used for preparing the *Echinacea* products and the final products can contain powdered plant parts, dry and liquid extracts, pressed and dried pressed juice (Barnes et al., 2010).

10. The composition of bioactive compounds varies across the three medicinally used species and their respective plant parts. It is generally

considered that there is no single chemical or a clearly defined group of chemicals responsible for the activity of Echinacea. The combined effects of several groups of bioactive compounds, including alkylamides, caffeic acid derivatives, echinacoside, cichoric acid, cynarin, flavonoids, polysaccharides and alkenes, all contribute to the biological activity of Echinacea (Barnes et al., 2010). There is also no consensus of which of the chemical constituent(s) should serve as a standardisation marker for Echinacea preprations.

Existing authorisations for Echinacea products in the UK

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11. Herbal products containing *E. purpurea* (L.) Moench. (European Medicines Agency (EMA) 2014), *E. angustifolia* DC, radix (EMA 2012) and *E. pallida* (Nutt.) Nutt., radix have herbal medicinal licences in EU/EEA member states. In the UK, there are a range of *Echinacea* products holding a Traditional Herbal Registration (THR) from the MHRA under the THR scheme (for the list of products see Table 13 Appendix B). These products have been approved for the relief of the common cold symptoms and influenza type infections, symptomatic relief of minor skin conditions such as spots, pimples, and blemishes and relief of minor urinary complaints associated with cystitis in women based on traditional use only in adults and children over 12 years for a maximum duration of 10 days. None of these products are recommended for pregnant or lactating women. Although *Echinacea* dietary supplements are the focus of this paper, the products holding a THR are worth noting for reference to doses and preparations (for further information on doses and preparations of THR *Echinacea* products and EMA monographs please see Table 14 Appendix B). It should be noted, however, that food supplements may differ significantly from EMA or MHRA approved herbal medicinal preparations in terms of preparation, composition, quality, and manufacturing standards. Therefore, it may not be appropriate to directly read across findings from studies or monographs on licensed products to food supplements.

12. A Traditional Herbal Registration (THR) can only be granted by the MHRA following a formal application that meets all the required standards for quality, safety, evidence of traditional use, and other criteria as set out in the Human Medicines Regulations 2012 (HMR, 2012). The evidence of traditional use relates to the product having been in traditional medicinal use for a continuous period of at least 30 years, of which at least 15 years must be within the European Union (Part 7 HMR, 2012). The safety requirements are a bibliographic review of safety data together with an expert report on safety (Schedule 12, HMR, 2012).

European Medicines Agency (EMA) assessment reports and conclusions

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13. The EMA framework specifies that the main regulatory pathways for bringing an herbal medicinal product to market in EU Member States are traditional use registration or well-established use marketing authorisation. For traditional use, herbal medicinal products can be registered under Article 16a of Directive 2001/83/EC if they have been in medicinal use for at least 30 years, including 15 years within the EU. Evidence of efficacy is based on bibliographic and historical data, demonstrating plausible efficacy and safety, without requiring clinical trials. These products are intended for minor conditions suitable for self-medication and must not be administered by injection. For well-established medicinal use, herbal medicinal products qualify under Article 10a of Directive 2001/83/EC when their active substances have been in well-established medicinal use within the EU for at least 10 years, supported by scientific literature showing recognised efficacy and acceptable safety.

14. The EMA has published detailed assessment reports on three medicinally used species: E. purpurea (L.) Moench. (EMA, 2014), E. angustifolia DC, radix (EMA, 2012) and E. pallida (Nutt.) Nutt., radix (EMA, 2018). The EMA assessment reports include specifications for the herbal substances, such as active constituents and details on the herbal preparations themselves. In contrast, such specifications are not available for Echinacea-based foods and food supplements, making direct extrapolation from EMA conclusions challenging.

15. According to the EMA assessment report on *E. purpurea*, the European Pharmacopoeia defines the herbal substance as the dried, whole or cut flowering aerial parts of *E. purpurea* with a minimum of 0.1% combined caftaric and cichoric acids content. It is also stated that US Pharmacopeia requires at least 1.0% cichoric acid and 0.01% dodecatetraenoic acid isobutylamides on a dry basis, detailed in the *E. purpurea* aerial parts pharmacopoeia monograph. Furthermore, the EMA report details that major constituents of *E. purpurea* include caffeic acid derivatives (cichoric acid 1–5%, caftaric acid, minor feruloyl-tartaric acid), alkylamides (notably dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide), polysaccharides such as PS I (35 kDa) and PS II (450 kDa), and volatile oils (0.08 – 0.32%) including borneol, bornyl acetate, germacrene D, and caryophyllene (EMA, 2014). The herbal preparation for well-established use consists of expressed juice with drug extract ratio (DER) of 1.5 - 2.1:1 or the dried juice corresponding to expressed juice (EMA monograph, 2014).

16. The EMA assessment report on *E. angustifolia* specifies that, according to the European Pharmacopoeia, *Echinaceae angustifoliae* radix consists of the whole or cut, dried underground parts of *E. angustifolia* DC and must contain not less than 0.5 % echinacoside. The EMA report details that major constituents of *E. angustifolia* root include caffeic acid derivatives (1.0 – 1.4%), cynarin (0.12 – 0.14%), chlorogenic acid and cichoric acid. Alkylamides are present at about 0.5%, mainly as isobutylamides and 2-methylbutylamides of straight-chain fatty-acids with olefinic and/or acetylenic bonds e.g. isomeric dodeca-2E,4E,8Z,10E/Z-tetraenoic isobutylamide. The root also contains polysaccharides and glycoproteins, including two polysaccharides (128 kDa and 4.5 kDa) and three glycoproteins (17–30 kDa), with the dominant sugars being arabinose (64–84%), galactose (2–5%), and glucosamine (6%). Volatile oils occur in small amounts (~0.1%) and include dodeca-2,4-diene-1-yl isovalerate and pentadeca-1,8Z-diene. Other constituents include phytomelanin and trace levels of saturated pyrrolizidine-type alkaloids (tussilagine and isotussilagine, approximately 0.006%) (EMA, 2012). The herbal preparation for traditional use consists of comminuted or powdered herbal substance, tincture (ratio of herbal substance to extraction

solvent 1:5) or liquid extract (DER 1:1). Both tincture and liquid extract are obtained with 45% v/v ethanol extraction solvent (EMA monograph, 2012).

17. The EMA assessment report on *E. pallida* states that, according to the European Pharmacopoeia, *Echinaceae pallidae* radix consists of the whole or cut, dried underground parts of *E. pallida* (Nutt.) Nutt and must contain not less than 0.2% echinacoside in the dried drug. Its major constituents are phenylpropanoids, particularly caffeic acid derivatives such as echinacoside (0.5–1.0%), chlorogenic acid, isochlorogenic acid, cynarin, and minor amounts of caftaric and cichoric acids. Unlike other species, alkylamides are essentially absent (approximately 0.001%). The root also contains phytomelanin, polysaccharides and glycoproteins, volatile oils (0.2–2.0%) including polyenes, polyacetylenes, ketoalkenes, and ketoalkenynes (EMA, 2018). The herbal preparation for traditional use consists of dry extract (DER 4-8:1) or tincture (ratio of herbal substance to extraction solvent 1:5), both obtained with 50% v/v ethanol extraction solvent (EMA monograph, 2018).

18. Studies on reproductive toxicity, genotoxicity and carcinogenicity had not been performed for preparations of *E. pallida* (EMA, 2018) or *E. angustifolia* (EMA, 2012) at the time the EMA reports were written. In the absence of these data, the use of these species in pregnancy and lactation was not recommended by EMA. Due to the lack of genotoxicity data, the EMA did not recommend the addition of *E. pallida* (EMA, 2018) and *E. angustifolia* (EMA, 2012) to the Community list of herbal substances, herbal preparations and combinations thereof for traditional medicinal products. There were also insufficient clinical data to support the criteria for well-established medicinal use of E. angustifolia and E. pallida roots, in accordance with Directive 2001/83/EC. The traditional use of *E. angustifolia* and *E. pallida* root extracts for the relief of common cold symptoms was deemed as acceptably safe by EMA due to longstanding history of use without reports of serious adverse effects.

19. *E. purpurea* is on the Community list of herbal substances, herbal preparations and combinations thereof for traditional medicinal products based on traditional topical use for the treatment of small superficial wounds (HMPC, 2007). The benefit-risk assessment, conducted by EMA, concluded that there was sufficient clinical evidence to support the well-established medicinal use, in accordance with Directive 2001/83/EC, of expressed juice preparations from *E. purpurea* fresh herb for the short-term prevention (maximum 10 days) and treatment of common cold in adults and children over the age of 12 (EMA, 2014).

20. No genotoxic or mutagenic effects have been observed in bacterial reverse mutation tests, human lymphocyte assay and micronucleus assay with lyophilised *E. purpurea* (EMA, 2014). There were limited epidemiological data suggesting no adverse effects associated with oral *E. purpurea* use and pregnancy outcomes (EMA, 2014). However, the EMA did not recommend its use (both topical and oral) during pregnancy and lactation due to the lack of guideline-conforming preclinical data on reproductive and developmental toxicity.

Health-based guidance values (HBGVs)

In this guide

21. There are currently no health-based guidance values (HBGVs) with respect to *Echinacea* or its constituents.

Toxicokinetics

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22. The EMA assessment reports on *E. purpurea* (EMA, 2014) and *E. angustifolia* (EMA, 2012) note that available pharmacokinetic data are limited and primarily focus on alkylamides and, to a lesser extent, caffeic acid conjugates. According to the human pharmacokinetic studies reviewed in the EMA reports, the alkylamides from *E. purpurea* and *E. angustifolia* show good oral bioavailability with rapid absorption and measurable plasma concentration within 20 - 60 minutes post-ingestion. The reported peak plasma concentration Cmax values for alkylamides varied between studies from 0.04 ng/mL for *E. purpurea* alkylamides (Goey *et al.*, 2012) to over 300 ng/mL for *E. purpurea/E. angustifolia* alkylamides (Matthias *et al*., 2005a). The EMA highlighted that these discrepancies are likely due to differences in the alkylamide profiles between *Echinacea* species, extract concentrations, analytical methods, and study design. Caffeic acid derivatives were not detected in plasma after oral administration and their oral bioavailability was questioned by the EMA assessors (EMA, 2014). The key pharmacokinetic studies from the EMA assessment reports are briefly outlined below.

E. purpurea

23. In a small clinical study by Goey *et al*. (2012), three cancer patients (age and sex not specified) received 20 drops of a commercial *E. purpurea* extract (65% V/V ethanol extract of freshly harvested *E. purpurea* herb (drug extract ratio (DER) 1:12)) and roots (DER 1:11) three times daily for 14 days. After the dose in the morning of day 15, blood samples for pharmacokinetics of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (DTAI) were drawn at 0, 30, 60 and 120 min post dose. For all three patients the plasma concentration–time curves showed a similar time course with a maximum plasma concentration of DTAI (0.04–0.18 ng/mL) achieved at 30 minutes after ingestion. The authors stated that the findings indicated low systemic exposure to alkylamides after repeated oral dosing.

E. angustifolia

24. In a randomised, open-label, crossover study, 11 healthy subjects (5 men and 6 women aged 25–36 years) received a single oral 2.5 mL dose of a 60% ethanolic extract from *E. angustifolia* roots (Woelkart *et al*., 2005). The maximum plasma concentration of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (DTAI), the main alkylamides in *E. angustifolia* roots, of 10.88 ng/mL was reached at 30 minutes after the dose. The authors noted that highly lipophilic alkylamides

with no double and triple bond at the end of the fatty acid chain could not be detected in the blood.

E. angustifolia/E. purpurea

25. Eleven healthy volunteers, males and females aged 18-26 years received *Echinacea* orally (4 tablets, each containing extract equivalent to 675 mg of *E. purpurea* root plus 600 mg of *E. angustifolia* root prepared from the dried ethanolic extracts of the two *Echinacea* species, which equals to a total dose of 2,700 mg *E.purpurea* root and 2,400 mg *E.augustifolia* root) immediately after a high fat breakfast (n=9) or fasted state (n=2) (Matthias *et al*. 2005). Blood samples were taken prior to tablet ingestion as well as 0.33, 0.66, 1.0, 1.33, 1.66, 2.0, 2.5, 3.0, 3.5, 4, 6, 8, 10, and 12 h post dose. Caffeic acid conjugates could not be identified in any plasma sample at any time after tablet ingestion. Alkylamides were rapidly absorbed and were measurable in plasma 20 min after tablet ingestion and remained detectable for up to 12 h. The maximal concentrations for the sum of alkylamides in human plasma were reached within 2.3 hours post ingestion and averaged 336 +/- 131 ng/mL plasma. The authors reported that the presence of food did not appear to influence the rate of alkylamide uptake, as plasma concentrations in the fasted state were within the range observed in subjects who consumed *Echinacea* after a standard high-fat breakfast. They concluded that alkylamides from *Echinacea* preparations were orally bioavailable and their pharmacokinetics supported the three times daily regimen already recommended for *Echinacea.*

Effects on cytochrome P450 and P-glycoprotein

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26. Freeman and Spelman (2008) conducted a literature review and found no verifiable reports of drug–herb interactions involving Echinacea products. They noted that herbal remedies derived from E. purpurea appear to have a low potential for cytochrome P450 (CYP450)-mediated interactions. The authors further estimated that, given the risk of adverse events (approximately 1 in 100,000), the annual consumption of Echinacea doses (around 10 million), and the fact that most use is short-term, products containing E. purpurea (roots and/or aerial parts) do not pose a significant risk to consumers. Nevertheless, they concluded that although current evidence does not support the need for specific precautions when Echinacea is co-administered with prescription medications, a prudent clinical approach would be to monitor patients taking Echinacea concurrently with substrates of CYP3A4 or CYP1A2.

27. The in vitro studies identified as part of the literature search performed by the Secretariat suggest that Echinacea has the potential to inhibit CYP3A4 (Yale and Glurich, 2005; Modarai et al. 2010; Hellum et al. 2007; Husain et al., 2023), CYP1A2 (Yale and Glurich, 2005; Hellum et al. 2007), CYP2E1 (Raner et al. (2007), CYP2C9 (Yale and Glurich, 2005), CYP2C19 (Modarai et al., 2010) and P-glycoprotein (Husain et al., 2023; Hansen and Nilsen, 2009). Some of the in vitro

studies reported a positive association between the total alkylamide content of the Echinacea preparation and its ability to inhibit CYP3A4 (Modarai et al. 2010) and CYP1A2 (Raner et al. 2007).

28. A clinical study on human volunteers by Gorski (2004) found that E. purpurea root extract (Nature's Bounty) taken orally at 1,600 mg/day for 8 days was capable of causing significant changes in drug disposition by inhibiting CYP1A2 and intestinal CYP3A activity and by inducing hepatic CYP3A activity. This preparation contained greater than 1% phenols (caftaric acid, chlorogenic acid, echinacoside and chicoric acid). Gorski (2004) concluded that the modest change in the clearance of compounds metabolised by CYP1A2 is considered clinically significant as this can lead to increased toxicity of narrow therapeutic window drugs such as theophylline, which is a substrate for CYP1A2. The authors also speculated that other drugs metabolised by CYP1A2 such as cyclobenzaprine, tacrine, and clozapine can be affected by Echinacea co-administration.

29. Another human study with 12 healthy volunteers (6 men, 6 women) investigated the effects of E. purpurea (800 mg, twice daily) for 28 days on CYP1A2, CYP2D6, CYP2E1 and CYP3A4 phenotypes (Gurley et al., 2004). The composition of the Echinacea preparation was analysed using HPLC and it was determined that it contained 13.7 mg chicoric acid per capsule, providing a daily dose of 43.8 mg chicoric acid. The administration of E. purpurea did not significantly change the activities of CYP3A4, CYP2E1, and CYP2D6 as estimated by comparing the phenotype ratios before and after treatment. Co-administration of E. purpurea caused an approximately 13% decrease in the ratio of paraxanthine/caffeine, suggesting that there was a possible inhibitory effect on CYP1A2 enzyme. However, the difference was not statistically significant and the authors did not think it was clinically relevant (Gurley et al., 2004).

Drug-herb interactions

30. Khaksary Mahabady *et al*. (2006) assessed whether *E. purpurea* extract or levamisole could reduce phenytoin-induced cleft palate in NMRI mice. Thirty-two pregnant NMRI mice were divided into four groups: saline control (10 mL/kg), phenytoin only (65 mg/kg), phenytoin (65 mg/kg) + levamisole (10 mg/kg), and phenytoin (65 mg/kg) + *E. purpurea* extract (360 mg/kg). All drugs were administered intraperitoneally from the first day of gestation, which was assumed to be upon the discovery of vaginal plug following mating. The study reported that phenytoin alone caused cleft palate in 16% of foetuses, while levamisole and *E. purpurea* reduced this to 5.3% and 3.2%, respectively. Foetal weight and length were significantly reduced in the phenytoin group but

remained normal in the treatment groups. The authors concluded that the observed protective activity of levamisole and *Echinacea* against phenytoin-induced cleft palate was due to immunomodulating and anti-inflammatory effects of these agents.

Annex A to TOX/2026/11

Reproductive and developmental studies on Echinacea

In this guide

Animal studies

31. There are no OECD guideline conforming in vivo studies on the reproductive and developmental toxicity of medicinally used Echinacea species. There are several studies investigating the effects of E. purpurea during pregnancy in mice (Barcz, E. et al., Chow et al., 2006) and pigs (Maass et al., 2005). The reproductive and immune parameters of E. pallida were investigated in pregnant rabbits (Dabbou et al., 2016) and their offspring (Kovitvadhi et al., 2016). No studies were found on the reproductive effects of E. angustifolia. The animal studies describing the reproductive and developmental effects of Echinacea are outlined below.

E. purpurea

32. Chow et al. (2006) investigated the potential association between E. purpurea consumption and spontaneous abortion in pregnant DBA/2 mice. Pregnant DBA/2 mice were randomised on the day a vaginal plug was detected to receive either E. purpurea–supplemented chow (n = 6) or standard Purina mouse chow (n = 7). An additional group of non pregnant mice (n = 7) received standard chow. The Echinacea supplemented diet was prepared by homogenising a commercially produced E. purpurea extract into finely ground standard chow, ensuring that individual mice consumed 0.45 mg/kg bw/day of the extract until they were killed (gestation days 10-14).

33. The study reported that Echinacea-fed mice showed reduced spleen lymphocytes and nucleated erythroid cells, aligning with levels in non-pregnant mice, whilst the bone marrow parameters were not influenced by the Echinacea supplementation. Although early pregnancy (days 10 – 11) showed no significant difference in foetal count, by days 12 – 14, only 50% of foetuses survived in the Echinacea group compared to controls (4.0/pregnancy in controls vs 2.0/pregnancy in Echinacea treatment group). The authors concluded that Echinacea may increase miscarriage risk in early pregnancy and advised against its use during this period.

34. Barcz et al. (2007) aimed to investigate whether pharmaceuticals containing dessicated alcoholic extracts of E. purpurea given to pregnant Balb/c mice influence the number, angiogenic activity and tissue vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in their foetuses. Eight female mice received 0.6 mg E. purpurea extract (see paragraph 35 for details) via an Eppendorf pipette from the 1st day of fertilization until the 18th day of pregnancy. Four mice were given vehicle control. On day 18, females were

sacrificed and the foetuses were extracted, counted, weighed and homogenised for angiogenic assessment. Angiogenic activity was evaluated by injecting the homogenate into two to three Balb/c mice and counting newly formed blood vessels on the inner skin surface. VEGF and bFGF concentrations in the homogenates were quantified using ELISA.

35. Within the experimental group, different E. purpurea formulations were used: three mice were given Esberitox, two received Immunal, and three received Echinapur. The authors did not report the compositions of these formulations. Based on an online search conducted by the Secretariat, Esberitox contains 3.2 mg dry extract (4–9:1) from a mixture of wild indigo rootstock, purple coneflower root, pale coneflower root, and arbor vitae tips and leaves (4.92:1; 85:1; and 85:1) per tablet; Immunal contains 1,140 mg of dry extract from fresh E. purpurea herb (1:12) and 60 mg of dry extract from fresh E. purpurea root (1:11) per tablet; and Echinapur contains 100 mg of thick extract from E. purpurea herb (DER 30–40:1; extractant: ethanol 23–30% v/v).

36. Barcz et al. (2007) reported that Echinapur and Esberitox groups showed a non-significant reduction in mean litter size compared to controls. However, all Echinacea treatments significantly reduced foetal VEGF and bFGF levels compared to controls ($p < 0.0001$). The angiogenic activity of the tissue homogenates, expressed as mean number of blood vessels, increased significantly in the Esberitox group, decreased in the Immunal group, and remained unchanged with Echinapur. The authors concluded that E. purpurea preparations may influence foetal angiogenesis and should not be recommended in pregnancy without further studies being carried out.

37. Maass et al. (2005) evaluated the effects of dietary E. purpurea in pregnant sows from day 85 of gestation to day 28 of lactation. Thirty-six sows were divided into three groups receiving 0%, 1.2%/0.5%, or 3.6%/1.5% Echinacea during pregnancy/lactation. The Echinacea supplement consisted of ground cobs made from the dried and pressed aerial parts of E. purpurea. Two batches were used, with constituent levels varying due to processing and storage: in the first batch, cichoric
acid declined from 420 to 290 mg/100 g plant dry matter and alkamides from 67.5 to 10.7 mg/100 g dry matter over the study period, while the second batch contained 170 mg/100 g dry matter cichoric acid and 44.1 mg/100 g dry matter alkamides. The study reported that Echinacea supplementation had no measurable effect on maternal liver enzyme activity (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase) or on haematological parameters, with no statistical differences

observed between supplemented and control sows in leukocytes, erythrocytes, lymphocytes, granulocytes, neutrophils, eosinophils, basophils, or monocytes. Colostrum crude protein content was 5% lower in the higher-dose Echinacea group compared with controls, although this difference was not statistically significant ($p = 0.11$). Maternal daily weight gain during gestation was 18% higher in the control group than supplemented groups, but weight loss during lactation did not differ between groups. Regarding offspring outcomes, piglet birth weight in the control group was 4% lower than in the Echinacea-supplemented groups, although this difference was not significant, and no significant differences were observed in the growth performance of suckling piglets.

E. pallida

38. Two linked studies investigated the effects of E. pallida supplementation in rabbits. In the first study (Dabbou et al., 2016), 100 pregnant does were fed either a standard diet or one supplemented with 3 g per kg of diet E. pallida from insemination to weaning. The Echinacea preparation contained caftaric acid, chicoric acid, chlorogenic acid and echinacoside with echinacoside found to be the main caffeic acid derivative. The study reported no differences between Echinacea supplemented and control does in maternal body weight at kindling, kindling rate, or blood morphology parameters, with red and white blood cell indices, platelet measures, and serum biochemical markers (total protein, glutamic oxaloacetic transaminase, blood urea nitrogen, albumin, urea, and cholesterol). Basophil counts were slightly reduced in the supplemented group, but this difference was not statistically significant. Regarding offspring outcomes, litter size at birth and at days 21 and 35, as well as kit mortality, did not differ between groups. Overall, the authors concluded that supplementation with E. pallida did not produce any significant effects on reproductive, haematological, or immune parameters in does.

39. The second study (Kovitvadhi et al., 2016) assessed the offspring of these does. Eighty weaned kits were allocated into four groups based on maternal diet and post-weaning diet: (1) offspring from control does fed the control diet, (2) offspring from control does fed the Echinacea supplemented diet, (3) offspring from Echinacea-supplemented does fed the control diet, and (4) offspring from Echinacea-supplemented does fed the supplemented diet. The diets consisted of a commercial basal feed with or without E. pallida supplementation (3 g per kg of diet). Parameters measured included growth, microbiome composition, blood biochemistry, phagocytic activity, and humoral immune response. The study reported that there were no significant differences in growth performances, blood parameters, bacterial community, or humoral immune response in the offspring.

Human studies

40. Human data on Echinacea use during pregnancy are limited and primarily based on observational studies and surveys. Two prospective studies (Gallo et al., 2000; Heitmann et al., 2016) reported no increased risk of major malformations, adverse pregnancy outcomes, or effects on birth weight or gestational age among women who used Echinacea, although information on species, preparation, dose, and duration was often incomplete. Survey data (Cuzzolin et al., 2010; Nordeng et al., 2011) also found no association between Echinacea use during pregnancy with adverse maternal or infant outcomes. Overall, the available human studies do not indicate adverse effects associated with use of Echinacea during pregnancy, but are limited by small sample sizes, reliance on self-reported use, lack of exposure characterisation, and potential confounding factors.

41. A prospective controlled study by Gallo et al. (2000) involving 206 pregnant women, enrolled and prospectively followed up after contacting the Motherisk Program, assessed the safety of Echinacea use during pregnancy. The study group was matched to a control group by disease (upper respiratory tract ailments), maternal age (±2 years), alcohol use, and cigarette use. The control group consisted of pregnant women who had contacted the Motherisk Programme regarding the safety of Echinacea for an upper respiratory tract ailment but subsequently did not use it or used a nonteratogenic antibiotic instead. In the study group, 112 women (54%) used Echinacea in the first trimester, with 17 (8%) exposed in all 3 trimesters. A total of 114 (58%) of 198 respondents used capsule or tablet preparations, or both, of Echinacea (250 to 1000 mg/d); 76 (38%) of the subjects used tinctures (5 to 30 drops per day). The self-reported duration of use was between 5 and 7 days. Different brands of E. purpurea and E. angustifolia were used, but the number of women using each species was not specified; E. pallida was only used by one woman. The study reported no significant differences between Echinacea users and controls in terms of pregnancy outcomes, including birth weight, gestational age, or malformation rates. Among Echinacea users, there were 195 live births, 13 spontaneous abortions, and 1 therapeutic abortion; the control group had similar outcomes (198 live births, 7 spontaneous abortions, and 1 therapeutic abortion). The authors stated that the malformation rates between Echinacea users and controls were also comparable, leading them to conclude that Echinacea use during organogenesis did not increase the risk of major malformations.

42. Heitmann et al. (2016) conducted a large prospective cohort study within the Norwegian Mother and Child Cohort, including 68,522 pregnancies after

exclusion of multiple births and chromosomal abnormalities. Maternal characteristics and potential confounders such as age, pre pregnancy BMI, folic acid use, smoking, education, previous pregnancy loss and year of delivery were adjusted for in the analyses using generalised estimating equations (GEE) models. Among the participants, 363 women (0.5%) reported using Echinacea during pregnancy, most commonly for treatment of respiratory tract infections. Echinacea supplements were taken during early (206 women) and late (183 women) pregnancy, though timing details were incomplete, and dosage/preparation were unspecified. The study reported that no increased risk of adverse maternal or pregnancy outcomes was observed in Echinacea users, and users did not show higher rates of preterm birth, low birth weight, or small for gestational age infants. Similarly, no increased risk of malformations was detected amongst the women who had used Echinacea during early pregnancy compared to controls; adjusted OR (95% CI) = 1.1 (0.6–2.1). There was 1.5% prevalence of major malformations in the women who had used Echinacea compared with 2.6% in the non-exposed group; adjusted OR (95% CI) = 0.6 (0.2–1.8). The three cases of major malformations that were detected among the Echinacea users were hypospadias, cleft lip, and hypoplastic left heart syndrome.

43. Cuzzolin et al. (2010) conducted a 10-month survey of 392 Italian women in maternity wards, using structured, face-to-face interviews to collect information on herbal product use during pregnancy, along with maternal health history and newborn outcomes. A total of 109 women (27.8%) reported using at least one herbal remedy during pregnancy, with 37.8% of them using herbal products throughout the entire gestational period. Echinacea was used orally by 10 women (9.2% of herbal users) for colds, anxiety, and immune support, although no details on species, plant part, preparation type, dosage, timing or duration were provided. By examining each herb descriptively, the authors reported one case in which prolonged Echinacea intake was possibly associated with intrauterine growth restriction in a 35 week newborn, although no further clinical details were provided for that case. The authors noted that the sample size limited the statistical analysis, resulting in all herbal products being treated as a single exposure group without distinguishing individual herbs and their separate effects on the pregnancy outcomes.

44. Nordeng et al. (2011) administered a structured questionnaire to 600 women within five days after delivery at Stavanger University Hospital Norway in order to investigate the use of herbal medicines in pregnant women in relation to pregnancy outcomes. In this cohort, 40% of women reported to have used herbal medicines during pregnancy, with Echinacea being used by 45 (7.5%) of those interviewed for cold and flu symptoms. No details were provided on Echinacea

species, dosage, or timing. In their analysis, the authors evaluated potential confounding factors through multivariable linear and logistic regression models, adjusting for maternal age, parity, education, marital status, gestational length, and conventional drug use, although some important confounders such as smoking and pre pregnancy BMI were not available. In this study, Echinacea use during pregnancy was not associated with adverse effects on birthweight, gestational age, mode of delivery, or neonatal complications.

Lactation

45. A case study examined the bioavailability of Echinacea alkylamides in human breast milk in a 35 year old volunteer at six different time points after ingestion of four Echinacea Premium tablets (Matthias et al., 2008). The tablets were prepared from dried ethanolic extracts of two Echinacea species and each tablet contained the equivalent of 675 mg E. purpurea root and 600 mg E. angustifolia root. A total of 13.1 mg of N-isobutyldodeca-2E,4E,8Z,10E/Z-tetraenamide alkylamides were ingested by the volunteer and they were found in the breast milk between 1 and 4 hours after the administration of the Echinacea tablets. Further details were not present in this conference abstract.

Maternal life history stages covered by reproductive and developmental studies

46. In order to identify any data gaps within the reproductive and developmental window when considering the safety of Echinacea in the maternal diet, the maternal life history stages covered by the animal and human studies discussed above are summarised in Table 1. Further information on the maternal life history stages, including their definition, can be found in the Scope of the Nutrition and maternal health project Annex. The terms insufficient, limited and adequate are used to describe the degree to which the study addresses and provides relevant data for the specific maternal life history stage. It must be noted that none of the studies are compliant with OECD guidelines.

Table 1: Maternal life history stages covered by available Echinacea animal and human studies

Study reference	**Study type**	***Echinacea* preparation and dose**	**Stage A (pre-mating to conception)**	**Stage B (conception to implantation)**	**Stage C (implantation to parturition - pregnancy)**	**Stage D (post-partum includi lactatio**
Chow *et al*. 2006	Animal study (DBA/2 mice)	*E. purpurea* extract 0.45 mg/kg bw/day (dose per body weight)	Insufficient	Limited	Limited	Insuffici
Barcz *et al*. 2007	Animal study (Balb/c mice)	*E. purpurea* extract 0.6 mg/day	Insufficient	Limited	Limited	Insuffici
Maass et al., 2005)	Animal study (pigs)	*E. purpurea* dried cobs 0.5-3.6%	Insufficient	Insufficient	Limited	Adequat
Dabbou *et al*., 2016	Animal study (rabbits)	*E. pallida* 3 g/kg	Insufficient	Adequate	Adequate	Adequat
Kovitvadhi *et al*., 2016	Animal study (rabbits)	*E. pallida* 3 g/kg	Insufficient	Insufficient	Insufficient	Adequat
Gallo *et al*., 2000	Human prospective controlled study	*E. purpurea* and *E. angustifolia* 250- 1000 mg/day	Insufficient	Insufficient	Limited	Insuffici

Heitmann *et al.*, 2016	Human prospective cohort study	Not specified	Insufficient	Insufficient	Limited	Insuffici
Cuzzolin *et al.*, 2010	Human cross-sectional study	Not specified	Insufficient	Insufficient	Limited	Insuffici
Nordeng *et al.*, 2011	Human cross-sectional study	Not specified	Insufficient	Insufficient	Limited	Insuffici
Matthias *et al.*, 2008	Human case report	Four tablets each containing *E. purpurea* 675 mg and *E. angustifolia* 600 mg	Insufficient	Insufficient	Insufficient	Limited

Toxicity Studies

In this guide

4. Annex A to TOX/2026/11 - Health-based guidance values (HBGVs)
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7. Annex A to TOX/2026/11 - Reproductive and developmental studies on Echinacea
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Cytotoxicity

E. purpurea

47. Tsai et al. (2012a) investigated the cytotoxicity of E. purpurea flower extract and its bioactive constituent chicoric acid in human colorectal cancer cell lines (HCT-116 and Caco-2). Treatment with Echinacea extract (0 – 2,000 µg/mL) for 24 hours did not affect cell viability, but a dose-dependent reduction was observed at 48 hours. Chicoric acid significantly decreased cell viability at ≥150 µg/mL after 24 hours and at all tested concentrations (50–200 µg/mL) after 48 hours. In HCT-116 cells, chicoric acid (50–150 µg/mL) suppressed telomerase activity, induced DNA fragmentation, activated caspase-9, and promoted PARP cleavage, indicating apoptosis. The authors concluded that the possible in vitro cytotoxicity mechanism of E. purpurea extract is mediated by repression of telomerase activity, activation of caspase pathway and induction of apoptosis.

E. angustifolia

48. The cytotoxicity of ethyl acetate extract of E. angustifolia was evaluated against two cancer cell lines MDA-MB-231 (ATCC HTB-26) and MCF-7 (ATCC HTB-22) and a healthy breast epithelial cell line MCF-10 (ATCC) using an 3-4,5-dimethylthiazol2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell viability assay (Espinosa-Paredes et al., 2021). The extract contained 11.2 µg/mg echinacoside and 8.18 µg/mg caffeic acid. The study reported that the E. angustifolia extract showed no cytotoxicity toward the healthy MCF 10 cells, whereas it reduced cell viability in both cancer cell lines, with calculated IC_{50} values between 16.3 and 28.8 µg/mL and no significant differences between 24 h and 48 h time points. The study also concluded that the E. angustifolia extract induced cell cycle arrest in the G1 phase and caspase-mediated apoptosis.

Acute toxicity

E. purpurea

49. A single high dose study reported no deaths or signs of toxicity following oral or intravenous administration of E. purpurea expressed juice to Wistar rats and NMRI mice (Mengs et al., 1991). No abnormalities were seen during a 14 day observation period or during necropsy, and an LD_{50} could not be determined.

E. angustifolia

50. A single dose study, compliant with the Organisation for Economic Co-operation and Development test guideline (OECD TG) 432, reported no clinical signs, mortality, or macroscopic lesions after the administration of 2,000 mg/kg bw of E. angustifolia ethyl acetate extract to three male CD-1 mice (Espinosa-Paredes et al., 2021). The extract contained 11.2 µg/mg echinacoside and 8.18 µg/mg caffeic acid. The authors classified the LD50 of the E. angustifolia extract as Category 5 under the Globally Harmonized System (GHS) (>2,000–5,000 mg/kg), indicating very low acute toxicity.

Sub-acute toxicity

E. purpurea

51. Expressed juice from E. purpurea was administered via oral gavage to groups of 18 Wistar rats per sex at doses of 0, 800, 2,400, or 8,000 mg/kg body weight daily for four weeks (Mengs et al., 1991). A statistically significant

reduction in plasma alkaline phosphatase was observed in males at 2,400 and 8,000 mg/kg, while females exhibited a significant increase in prothrombin time at the same dose levels compared to controls. The authors concluded that since the alkaline phosphatase and prothrombin time were still in the normal physiological variation range for the rat strain used and there was no dose dependent response, no toxicological point of departure could be derived from the data. The study reported that all other parameters, including biochemical and haematological results, body weight, food consumption, ophthalmological findings, necropsy, and histopathology, showed no significant differences among treatment groups. The authors stated compliance with the OECD GLP principles and to OECD recommendations for technical methods, although no specific OECD TG applicable to the subacute toxicity study was referenced.

E. angustifolia

52. Espinosa-Paredes et al. (2021) conducted a 28-day repeated-dose toxicity study with ethyl acetate extract of E. angustifolia. The extract, containing 11.2 µg/mg echinacoside and 8.18 µg/mg caffeic acid, was administered to five CD-1 mice per dose per sex at 20 mg/kg bw or 200 mg/kg bw in accordance with the OECD TG 407. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine levels were determined. No statistically significant differences were observed between treated and control groups, and the authors concluded that there was no evidence of liver or kidney toxicity associated with the E. angustifolia extract.

Sub-chronic toxicity

E. purpurea

53. The toxicity of E. purpurea extract was evaluated in a 13-week repeated oral dose toxicity test in Sprague Dawley rats (Jeong et al., 2024). The study was conducted in accordance with Good Laboratory Practice (GLP) regulations and Test Guidelines of Standards for Toxicity Studies of Drugs issued by the Korean Food and Drug Administration. The E. purpurea extract, standardised to contain at least 2% chicoric acid, was administered daily at doses of 0, 500, 1,000, and 2,000 mg/kg body weight to groups of 10 rats per sex. No mortality or abnormal clinical signs were observed in either sex at any of the tested doses. The study reported that the ophthalmological examinations, absolute and relative organ weights, haematology, and serum biochemistry showed no significant differences

between treated and control groups. The urinalysis revealed a statistically significant increase in mean urine volume in males at 1,000 mg/kg compared to controls. Some individual variations were also observed in the urinalysis, but the study concluded they were not significantly different when compared to the controls.

Genotoxicity

E. purpurea

In vitro genotoxicity assays

Bacterial reverse mutation tests

54. A lyophilised Echinacin Liquidum herbal medicinal product (E. purpurea) was evaluated for mutagenic potential in an in vitro bacterial reverse mutation assay using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, with and without S9 metabolic activation, at concentrations ranging from 8 to 5,000 µg/plate (Mengs et al., 1991). The test material, the bacterial strains and S9 mix were incorporated into molten agar, poured onto minimal agar plates and incubated at 37°C for three days. The authors reported that across three replicates, mean revertant counts showed no reproducible, statistically significant or dose related increases in any strain, with or without metabolic activation. Since no positive response was observed at any concentration up to the limit dose of 5,000 µg/plate, the study concluded that the tested product exhibited no mutagenic potential. The study stated compliance with OECD GLP principles and OECD technical recommendations, although no specific OECD TG applicable to the bacterial reverse mutation test was referenced.

55. The mutagenicity and the antimutagenic effects of freeze dried E. purpurea 50% ethanolic extracts were evaluated in S. typhimurium TA98 and TA100 strains with and without S9 metabolic activation at a maximum concentration of 5,000 µg/plate (Tsai et al., 2012b). The ethanolic extracts contained caftaric acid, chlorogenic acid, echinacoside and cichoric acid, but no cynarin. For the mutagenicity assay, the bacteria were mixed with 250-5,000 µg/plate of the extract, incubated on histidine containing media at 37°C for 48 h and revertant colonies were compared with vehicle controls. The study reported that the E. purpurea extract did not induce any significant increases in revertant numbers in either strain, at any concentration under any condition, when compared to control plates treated with dimethyl sulfoxide (DMSO). The authors also assessed

antimutagenic activity of the extract by calculating the percentage inhibition of the reversion rate in the presence of 2 aminoanthracene and reported that the E. purpurea extract demonstrated a dose dependent inhibitory effect on 2 aminoanthracene induced mutagenicity in both S. typhimurium strains. There was no indication as to whether the bacterial reverse mutation test had been conducted in compliance with OECD TG.

56. E. purpurea extract standardised to contain at least 2% chicoric acid was tested in an in vitro bacterial reverse mutation test in S. typhimurium strains TA98, TA100, TA1535 and TA1537 and tryptophan auxotroph mutant Escherichia coli strain (WP2uvrA) in accordance with OECD TG 471 (Jeong et al., 2024). The bacterial strains were incubated with the E. purpurea extract at up to 5,000 µg/plate with and without S9 mix, for 48 hours at 37°C. Sodium azide, 2-nitrofluorene, 2-aminoanthracene, aminoacridine and 4-nitroquinoline N-oxide were used as positive controls and water was used as negative control. The authors stated that the number of mutant colonies at all doses of each strain did not exceed twice that of the negative control and results were considered negative for mutagenicity.

Mouse lymphoma assay

57. A lyophilised Echinacin Liquidum herbal medicinal product (E. purpurea) was evaluated for its potential to induce mutations at the hypoxanthine phosphoribosyltransferase (HPRT) locus of L5178Y mouse lymphoma cells, both in the presence and absence of S9 metabolic activation, at concentrations ranging from 50 to 5,000 µg/mL (Mengs et al., 1991). The cells were exposed to the test or control solution for 2 hours, then allowed a 7 day expression period before plating with and without 6 thioguanine to determine mutation frequency. A response was considered significant only if treated cultures exceeded the 95th percentile threshold of controls, occurred at consecutive doses, and showed a dose response by regression analysis. Cytotoxicity was assessed via plating efficiency immediately after treatment. The study reported that the Echinacea treatment did not produce a statistically significant increase in mutation frequency at any of the concentrations tested, with and without S9 metabolic activation, and that doses up to 5,000 µg/mL were considered essentially non toxic. The study stated compliance with the OECD GLP principles and OECD technical recommendations, although no specific OECD TG applicable to the mouse lymphoma assay were referenced.

Chromosomal aberration tests

58. Mengs et al. (1991) also tested the lyophilised Echinacin Liquidum herbal medicinal product (E. purpurea) in an in vitro cytogenetic assay using human lymphocyte cultures, with and without S9 metabolic activation, at concentrations ranging from 2,400 to 5,000 µg/mL. The cells were exposed to the test or control solution for either 20 or 44 h (without S9) or for 3 h followed by recovery (with S9), then analysed for mitotic index and chromosomal aberrations. The authors stated that no mitotic inhibition was observed at any concentration under any condition. A small but statistically significant increase in the proportion of cells with structural chromosomal aberrations was reported at 5,000 µg/mL at the 20 h sampling without S9. However, the authors considered this biologically insignificant because values remained within the laboratory's normal range and coincided with increased osmolality of the treatment medium. The study stated compliance with OECD GLP principles and OECD technical recommendations, although no specific OECD TG applicable to the chromosome aberration assay were referenced.

59. E. purpurea extract standardised to contain at least 2% chicoric acid was tested in an in vitro chromosomal aberration test using Chinese Hamster Lung (CHL/IU) cells in accordance with OECD TG 473 (Jeong et al., 2024). The cells were incubated with the E. purpurea extract at concentrations of 78.1, 156 and 313 µg/mL, in the presence or absence of S9, for either 6 or 24 hours for the short-term and continuous treatment, respectively. Mitomycin C at a concentration of 0.1 µg/mL and benzo[a]pyrene at 20 µg/mL were used as positive controls, whilst water was used as negative control. Microscopic slides for chromosomal observation were prepared, and chromosomal abnormalities were divided into structural and numerical aberrations. The study reported that no statistically significant increase in structural or numerical chromosomal aberrations was observed in the Echinacea treated cells compared to controls at any of the concentrations tested, with and without S9 metabolic activation.

In vivo micronucleus test

60. Mengs et al. (1991) conducted an in vivo micronucleus test using a single oral dose of 25,000 mg/kg Echinacin Liquidum (E. purpurea) via oral gavage to groups of 5 male and 5 female NMRI mice. The animals were sacrificed at either 24, 48 or 72 hours after the dose. Positive control groups received 100 mg/kg cyclophosphamide via intraperitoneal injection, and negative controls received 25 mL/kg water by oral gavage. Bone marrow was collected from the femur, and two smears per animal were prepared, fixed, and stained. One thousand polychromatic erythrocytes (PCE) per animal were scored microscopically for

micronuclei. The authors reported that the positive control showed a significant increase in the proportion of micronucleated PCE, whilst the Echinacea preparation did not show any statistically significant differences compared to the negative control. The PCE/NCE ratio was also not significantly different between treated and control groups. The study stated compliance with OECD GLP principles and applicable OECD technical recommendations, although it did not reference a specific OECD TG for the in vivo micronucleus test. Additionally, no toxicokinetic measurements were reported to demonstrate bone marrow exposure to the test substance.

61. E. purpurea extract standardised to contain at least 2% chicoric acid was orally administered at 1,250 and 5,000 mg/kg bw to seven-week-old male Sprague Dawley rats (5 animals per dose) in a vivo micronucleus test in accordance with OECD TG 474 (Jeong et al., 2024). Positive control groups received 20 mg/kg cyclophosphamide orally, and negative controls received water. Following the second dose, bone marrow was collected from the femurs, fixed, and stained with acridine orange for fluorescence microscopy. Genotoxicity was assessed by counting micronucleated polychromatic erythrocytes (MNPCE) among 4,000 PCE per rat, and cytotoxicity was evaluated based on the proportion of PCE among 500 red blood cells. Cytotoxicity indices were comparable across all groups. The study reported that the positive control produced a genotoxicity index approximately 100-fold higher than the negative control, whilst none of the Echinacea dose groups showed statistically significant differences in genotoxicity relative to the negative control. The authors also conducted a toxicokinetic study with pure chicoric acid and the standardised E. purpurea extract and noted that the pharmacokinetics of chicoric acid were comparable between the purified compound and the standardised E. purpurea extract, with similar simulated concentration–time profiles volume of distribution and clearance.

E. angustifolia

62. Espinosa-Paredes et al. (2021) conducted an in vitro bacterial reverse mutation test and an in vivo micronucleus test with E. angustifolia ethyl acetate extract containing 11.2 µg/mg echinacoside and 8.18 µg/mg caffeic acid. There is no indication as to whether these tests had been performed in accordance with the OECD TG.

63. For the bacterial reverse mutation assay, the bacterial strains S. typhimurium TA98, TA100 and TA102 were incubated with the E. angustifolia extract at up to 200 µg/plate, with and without S9 mix, for 48 hours at 37°C.

Picrolonic acid, 2-amino-anthracene, N-methyl-N′-nitro-N-nitrosoguanidine and mitomycin-C were used as a positive control, whilst DMSO was used as negative control. A test was considered positive when the number of spontaneous colonies exceeded twice the number of basal revertants. The authors reported that the tested concentrations of E. angustifolia extract, with or without S9 mix, did not yield a positive result and concluded no genotoxic activity was therefore observed.

64. For the in vivo micronucleus test, the E. angustifolia extract was administered intragastrically at 1,000 mg/kg bw to three male CD-1 mice. DMSO was used as a vehicle control, water as the negative control and cyclophosphamide (50 mg/kg) as the positive control. The animals were euthanised 48 hours after test substance administration, blood samples were collected, fixed and labelled prior to flow cytometry analysis. The frequencies of normochromatic erythrocytes (NCEs) and reticulocytes (RETs), with and without micronuclei (MNs), were evaluated in order to calculate the percentages of mature normochromatic erythrocytes (% MN-NCEs), micronucleated reticulocytes (% MN-RETs) and total reticulocytes (% RETs). The study reported that the E. angustifolia extract did not induce a significant increase in micronuclei formation, with %MN-RET at 0.9% compared to 0.3% in the negative control. A decrease in the frequency of RET in the Echinacea extract group compared with the negative control (2.56% vs 5.41%, $p < 0.05$) was reported, but the authors did not comment on its biological relevance. No toxicokinetic measurements were reported to demonstrate bone marrow exposure to the test substance.

Adverse effects in humans

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7. Annex A to TOX/2026/11 - Reproductive and developmental studies on Echinacea
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65. The adverse effects of Echinacea preparations in humans have been described in several literature reviews, EMA assessment reports, individual case studies and pharmacovigilance data. Although these findings relate to the general population and not specifically to pregnant women or exposure through the maternal diet, they have been included to provide broader insight into the potential toxicities of Echinacea in humans, while acknowledging their limited relevance to pregnancy specific risk assessment.

66. The EMA assessment report on E. purpurea concluded that based on the analysis of pharmacovigilance reports from EU member states, hypersensitivity reactions such as rash, urticaria, itching and swelling were possible adverse effects of Echinacea and in a case of allergic reaction, Echinacea should not be taken again. The EMA report stated that there were cases of severe reactions such as Stevens-Johnson Syndrome, angioedema, bronchospasm, asthma and anaphylactic shock with confirmed/probable causality. The report acknowledged that cases of autoimmune diseases such as encephalitis disseminata, erythema nodosum, immunothrombocytopenia, Sjögren’s syndrome with renal tubular dysfunction were reported, but that their causality was inconclusive. The report further stated that gastrointestinal side effects reported were unlikely to be linked to Echinacea as their frequency was similar between the placebo and treatment groups in clinical trials (EMA, 2014).

67. A meta-analysis of six randomised controlled trials (Schapowal et al., 2015), evaluating various Echinacea preparations for respiratory tract infections, also reported on adverse events in 1,440 Echinacea treated participants and 1,326 placebo treated controls. Although the trials primarily assessed potential benefits, the safety data indicated no significant difference in the overall number of adverse events between Echinacea (491 events) and placebo (474 events). The Echinacea products used varied across studies, including ethanol/glycerol extracts of E. purpurea and E. angustifolia (500–4,000 mg extract/day) and pressed juices of E. purpurea (6,200–10,000 mg/day). Most reported adverse effects were mild, transient gastrointestinal disturbances. Two severe adverse events (stridor) occurred in the Echinacea group, and one severe event (glandular fever requiring hospitalisation) occurred in the placebo group. No significant differences in clinical biochemistry were observed. Although the meta-analysis also concluded that Echinacea may reduce respiratory tract infections, these findings are beyond the scope of the present assessment and only the safety data have been considered here to inform understanding of the potential adverse effects associated with Echinacea use in humans.

68. A systematic review summarised evidence of the safety of Echinacea based herbal medicinal products from 36 clinical studies, case reports, and spontaneous reporting programmes from regulatory agencies in Australia, Germany, UK, USA and Sweden (Huntley et al., 2005). The oral doses used in the clinical trials were typically 4-8 mL expressed juice/liquid extract twice daily, 250-1,000 mg daily in the form of capsules/tablets or 5-30 drops daily for the tinctures. The review concluded that Echinacea had a good safety profile when taken short-term, with short-term use being defined as ‘days as opposed to weeks’. Adverse effects were mild, transient and reversible with gastrointestinal disturbances and skin-related reactions being most commonly reported. The review discussed that in rare cases Echinacea use can be associated with allergic reactions, which can be severe. However, the authors noted that in about a quarter of these cases, Echinacin ® (E. purpurea) was administered intramuscularly or intravenously. Nevertheless, the authors suggested that atopic and asthmatic patients should be cautious when using Echinacea supplements.

69. An Australian study looking at adverse reactions associated with Echinacea reviewed 51 reports of adverse drug reactions (ADRs) in the Australian Adverse Drug Reactions Advisory Committee’s database (Mullins and Heddle, 2002). There were 26 cases which were suggestive of IgE-mediated hypersensitivity reactions (4 anaphylaxis, 12 acute asthma,10 urticaria/angioedema). Seventy eight percent of the affected patients were female, the median age was 32 years and over half

had a history of asthma, allergic rhinitis or atopic dermatitis. In addition to the review of the ADR reports, five cases of adverse reactions to Echinacea were personally evaluated by the authors. Two patients suffered anaphylaxis and a third had an acute asthma attack 10 minutes after their first ever dose of Echinacea. All three patients were female, had a history of atopy including allergic rhinitis or latex allergy and tested positive on skin prick tests to aqueous Echinacea. A fourth case described a 56-year-old man who developed recurrent mild asthma with Echinacea tablets, resolving upon discontinuation. The fifth case involved a 48-year-old woman who developed a maculopapular rash within two days of Echinacea tablets ingestion, recurring on rechallenge. Both latter patients had allergic rhinitis but negative skin prick test. The overall conclusion of the study was that there is a possible cross-reactivity between Echinacea and other environmental allergens and atopic patients should be warned accordingly (Mullins and Heddle, 2002).

70. There are individual case reports of adverse effects experienced by people after taking Echinacea preparations including an autoimmune disease supposedly triggered by Echinacea (Lee and Werth, 2004), isolated case of erythema nodosum in a 41-year old male (Lee Soon and Crawford, 2001), hypereosinophilia in a 58-year old male patient with history of asthma and allergic rhinitis (Maskatia and Baker, 2010), leucopenia in a 51 year old woman who took 450 mg Echinacea capsules for 2 months (Kemp and Franco, 2002), thrombocytopenia with E. pallida in a 32 year old man (George et al., 2006) and hepatotoxicity in a 45-year old male who took 1,500 mg Echinacea root for the treatment of cold (Kocaman et al., 2008). However, limited information was available in these case reports about the doses taken, and it was uncertain whether the adverse effects described were related to Echinacea consumption or to other factors, such as the use of other herbal products such as St John’s wort (Lee Soon and Crawford, 2001) or Gingko biloba (Kemp and Franco, 2002). In the case report of hepatotoxicity associated with Echinacea the authors concluded that this was a case of Echinacea-induced acute cholestatic autoimmune hepatitis (ACAH) due to the immunostimulatory effects of Echinacea (Kocaman et al., 2008).

Duration of use

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71. The EMA advises that oral Echinacea preparations should be used for a limited duration of up to 10 days (EMA, 2014). The German Commission E monographs on Echinacea recommend that internal and external administration of E. purpurea and E. pallida should not exceed 8 weeks (Blumenthal et al., 1999). However, some clinical studies (see paragraphs 72–74) report the use of Echinacea preparations for longer periods. It should be noted that these clinical studies typically involve medicinal Echinacea preparations, which may not be directly comparable to foods or food supplements that are the focus of this assessment.

72. The clinical studies involving Echinacea have varying durations from 4-21 days to 4-12 weeks (Ardjomand-Woelkart and Bauer, 2015). The study with the longest duration was prospective, placebo controlled, double blinded cross over trial in which participants (n=50) were randomised to receive 6 months of 800 mg

Echinaforce (95% E. purpurea whole plant extract and 5% E. purpurea root extract) twice daily or placebo, followed by the alternate treatment for a further 6 months for reducing the frequency and duration of recurrent genital herpes (Vonau et al., 2001). The only side effects reported were nausea (n = 4) and diarrhoea (n = 2). Pregnancy, or not using effective contraception during the study period, were exclusion criteria for this trial.

73. The use of E. purpurea and E. angustifolia root liquid extract for 12 weeks (100 drops daily of a 1:11, 30% ethanolic extract for 5 days a week) was studied in randomised, double-blind, placebo controlled trial involving 289 patients (n=100 for E. angustifolia, n=99 for E. purpurea, n=90 for placebo) for the prevention of respiratory tract infections (Melchart, 1998). The side effects reported included minor gastrointestinal symptoms, headache/dizziness, allergic reactions and were similar between treatment arm and placebo (Melchart, 1998).

74. The safety and efficacy of Echinaforce was tested in a large randomised, double-blind, placebo-controlled clinical trial for 4 months (Jawad et al., 2012). A total of 755 subjects were included and the main criteria for inclusion was that they experience ≥2 colds per year. Participants took the equivalent of 2,400 mg of extract a day for illness prevention, but during acute stages of colds the dose was increased to 4,000 mg extract/day. There were no significant differences between the frequencies and the type of adverse effects between treatment and placebo. Haematological and biochemical measures were not significantly different before and after Echinacea treatment and when compared to placebo.

Mechanism of action

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6. Annex A to TOX/2026/11 - Effects on cytochrome P450 and P-glycoprotein
7. Annex A to TOX/2026/11 - Reproductive and developmental studies on Echinacea
8. Annex A to TOX/2026/11 - Toxicity Studies
9. Annex A to TOX/2026/11 - Adverse effects in humans
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75. The exact mechanism of action of Echinacea preparations in relation to common cold symptoms is not known. Antiviral, immunomodulatory and anti-inflammatory effects of Echinacea have been reported in in vitro, in vivo and human studies referenced below. However, the relevance of the in vitro and in vivo effects of Echinacea to clinical efficacy is not known and the exact pharmacodynamic mechanism cannot be established (EMA, 2014).

Antiviral effects

76. The Echinacea antiviral mechanism of action is not fully elucidated, but it is thought to be due to prevention of viral entry into the cells rather than inhibition of viral replication (Pleschka et al., 2009; Sharma et al., 2009), suggesting that Echinacea treatment is effective only at the very early stages in the infection process (Pleschka et al., 2009). The use of different species, extraction methods and preparations make it difficult to attribute the antiviral activity of Echinacea to specific compounds. Echinacea has also been reported to inhibit the induction of pro-inflammatory cytokines IL-6, IL-8 and TNF-α in vitro (Sharma et al., 2009) and IL-10 and IFN-γ in vivo (Fusco et al., 2010). The authors suggested that this immunomodulatory activity may contribute to improved clinical outcomes by moderating the inflammatory response (Fusco et al., 2010).

Immunomodulatory and anti-inflammatory effects

77. The immunomodulatory properties of Echinacea and its constituents have been extensively studied and reviewed in the literature. The studies reviewed in this statement reported that Echinacea stimulated the secretion of TNF-α (Burger et al., 1997; Rinninger et al., 2002; Goel et al., 2002), IL-1(Burger et al., 1997; Rinninger et al., 2002; Zhai et al., 2007) and IL-10 (Burger et al., 1997; Li et al., 2017) from macrophages and IFN-γ from lymphocytes (Li et al., 2017; Zhao et al. 2007). Echinacea has also been shown to increase the natural killer cells (NK) mediated cytotoxicity (See et al., 1997; Gan et al., 2003; Zhao et al. 2007), promote dendritic cells maturation (Li et al., 2017) and lead to changes in the percentage of immune cell populations, including T lymphocytes and NK cells (Zhao et al. 2007; Li et al., 2017; Gan et al., 2003). The immunomodulatory effects of Echinacea from in vitro and animal studies have been summarised in Table 2. The majority of the studies focused on E. purpurea preparations, with the exception of Zhao et al. (2007) where E. angustifolia and E. pallida were also tested.

78. Echinacea extracts have also been reported to exhibit anti-inflammatory properties due to their ability to inhibit cyclooxygenases (COX) I and COX II (Clifford et al., 2002) and 5-lipoxygenase (5-LOX) (Merali et al., 2003). Clifford et al. (2002) found that alkylamides from E. purpurea roots inhibited COX-I and COX-II by 36–60% and 15–46%, respectively, at 100 µg/mL, compared to higher inhibition by standard non-steroidal anti-inflammatory drugs (NSAIDs). Merali et al. (2003) reported 5-LOX inhibition by root extracts of E. angustifolia, E. purpurea, and E. pallida attributing the activity to the presence of alkylamides in the extracts.

Table 2: Summary of the immunomodulatory effects of Echinacea

Echinacea **preparation**	**Concentration or dose**	**Test system**	**Summary of immune system effects**	**Reference**

Fresh and dried juice from EchinaFresh (*E. purpurea)* standardized for a content of 2.4% soluble β-1,2-D-fructofuranosides.	0.05-10 µg/mL fresh juice and 0.01-10 µg/mL dried juice.	Human peripheral blood macrophages	Statistically significant increase in the production of IL-1, TNF-α, IL-6 and IL-10 by the macrophages at all concentrations of *Echinacea.*	Burger *et al*., 1997
E. purpurea raw herb and root powders subjected to simulated digestion protocol in simulated gastric fluid.	5 – 320 µg/mL	RAW267.7 murine macrophages	Dose dependent induction of TNF-α, NO, IL-1α, IL-1β, and IL-6 with *Echinacea* treatment comparable to the results observed with the LPS positive control.	Rinninger *et al*., 2002

Plant parts extracted with aqueous ethanol, producing four different fractions with concentrations of chicoric acid, polysaccharide and alkylamides at basal level, 3, 20 and 50 times the basal level.	100 µL *via* oral gavage	Male Sprague-Dawley rats	*Echinacea* fractions at 20 and 50 times the basal dose levels significantly increased the phagocytic index in alveolar macrophages compared to basal and 3 times basal level dose. TNF-α secretion from alveolar macrophages showed a dose-dependent rise with 3 and 20 times basal level doses. Similarly, spleen macrophages exhibited dose-dependent increases in TNF-α and IFN-γ release.	Goel *et al*., 2002

Commercially available *E. purpurea* extracts with a defined chemical composition of chicoric acid (3.045%), caftaric acid (1.575%), chlorogenic acid (0.065%), dodeca-2E, 4E, 8Z, 10E/Z-tetraenoic acid isobutylamide (1.635%).	400 µg/mL	Bone marrow-derived dendritic cells (BMDCs) derived from femur and tibia of 6–8-week-old female C57BL/6 mice.	*Echinacea* treatment significantly increased percentage of CD40, CD80, CD83 and CD86 markers on BMDCs and increased the secretion of IFN-γ, IL-12, IL-10, and TGF-β1 by BMDCs. Endocytosis of fluorescently labelled dextran reduced by *Echinacea* treatment, similar to results observed with LPS control.	Li *et al*., 2017

Dried, ground preparations of fresh *E. purpurea* herb homogenized, filtered and used fresh the same day.	0.001 to 1000 pg/mL	Human peripheral blood mononuclear cells (PBMC) from healthy patients or patients with chronic fatigue syndrome (CFS) or acquired immunodeficiency syndrome (AIDS).	Significant increase in the NK cell activity from healthy patients and those with CFS and AIDS was observed following *Echinacea* treatment in a concentration dependent manner. A similar concentration dependent response was observed for the antibody dependent cell-mediated cytotoxicity in all three patient groups following *E. purpurea* treatment.	See *et al.*, 1997

			Increase in the NK-mediated cytotoxic activity was observed with *E. purpurea* treatment in a concentration dependent manner.	
E. purpurea dissolved in water and filtered to prepare a water soluble extract.	Concentrations up to 10 µg/mL	Human peripheral blood mononuclear cells (PBMC)	*Echinacea* treatment reduced CD16 expression (frequency and intensity) by lymphocytes, while increasing CD69 expression within $CD16^+$ populations, with over 90% $CD16^+$ cells expressing CD69 at the highest concentration.	Gan *et al*., 2003

Ground *E. purpurea* aerial parts and freeze dried into a powder. The preparation contained cichoric and caftaric acids, as well as cynarin, but not alkylamide.	Concentrations of up to 250 µg/mL	Human T-cell line Jurkat E6-1	*E. purpurea* induced a dose-dependent increase in IL-2 secretion and a five-fold rise of IFN-γ secretion by high-density T cells.	Fonseca *et al*., 2014

Alcohol extracts of *Echinacea*. *E. purpurea* contained chicoric acid and caftraic acid, no echinacoside. *E. angustifolia* contained echiancoside, cynarin, chlorogenic acid. *E. pallida* contained echinacoside, chlorogenic acid and caftaric acid.	130 mg/kg bw/day by gavage	Eight-week-old male BALB/c mice	All three *Echinacea* species increased IFN-γ production in mitogen-stimulated splenocytes, suppressed IL-1β and TNF-α. In non-stimulated splenocytes, *E. purpurea* significantly increased IL-1β secretion. *E. purpurea* increased the percentage of $CD49^+$ and $CD19^+$ splenic cells, while *E. angustifolia* only increased $CD49^+$; *E. pallida* had no effect on either. Only *E. pallida* significantly enhanced NK cell cytotoxicity.	Zhai *et al.*, 2007

Contaminants

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79. Very few studies, described below, have investigated the potential contaminants in Echinacea preparations, including heavy metals, moulds and mycotoxins.

80. From 1999-2004, 13,504 adults participated in National Health and Nutrition Examination Survey (NHANES) interviews, examinations and had their blood lead levels assessed (Buettner et al., 2009). The authors fitted a regression model for women of child-bearing age (16-45 years), which showed that those who used herbal supplements had adjusted blood lead levels 20% (95% CI 5%–34%, p = 0.008) higher than women who did not. However, when broken down by the specific herbal supplement, the difference was not significant for

Echinacea supplements (8%, 95% CI -15% – 35%, p = 0.55).

81. Filipiak-Szok et al., (2015) conducted a study measuring concentrations of heavy metals, including lead (Pb), cadmium (Cd), arsenic (As), aluminium (Al), nickel (Ni), barium (Ba), and antimony (Sb), in raw plant material of selected medicinally used herbs and dietary supplements available on the Polish market. These results were compared against the limits set by WHO (0.3 mg/kg for cadmium, 10 mg/kg for lead and 5.0 mg/kg for arsenic) and by the EU Commission Regulation (EC) No. 1881/2006 (1.0 mg/kg for cadmium and 3.0 mg/kg for lead). The levels found in the dried Echinacea purpurea samples were considerably lower with 0.02 mg/kg cadmium, 0.6 mg/kg lead and 0.16 mg/kg arsenic.

82. Another study analysed popular food supplements, including seven Echinacea containing brands, for the presence of heavy metals and microbial contamination (Raman et al., 2004). The supplements analysed were in the forms of tablets, capsules or soft gels. The authors determined the daily dose of each heavy metal that would be ingested if the supplement was taken as recommended by the manufacturer. Depending on the Echinacea brand, the daily doses of heavy metals would be: lead 0.034-2.901 µg/day, cadmium 0.004 – 0.967 µg/day, arsenic 0.027 – 0.908 µg/day, chromium 0.125-8.838 µg/day, and thallium 0.002 – 0.383 µg/day. Mercury was not detected in the samples. The authors compared these values to tolerable intake levels at the time of publication and concluded that the supplements do not pose a risk to consumers.

83. Alternaria alternata, Aspergillus spp., Fusarium spp., Phoma spp. and yeasts have been detected in Echinacea herbal supplements at 100-1,000 CFU/g with 71% of the Echinacea samples (n=7) harbouring fungi (Tournas, 2009). Twenty one samples were analysed as part of a study investigating the presence of moulds and their secondary metabolites in Echinacea dietary supplements available on the Polish market (Pilarska et al., 2022). It was found that 12 samples were contaminated with Aspergillus spp., whilst Eurotium and Penicillium spp. were detected in 8 of the samples. Mycotoxin contamination was found in 18 of the samples with zearalenone (18/21), deoxynivalenol (5/21) and T-2 (3/21) occurring at the highest frequencies.

Exposure Assessment

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84. *Echinacea* is not used as a food commodity on its own or in recipes for cooking, but there are tea and honey products, found from online sources, supplemented with *Echinacea* and *Echinacea* extracts (Appendix B, Table 7) and these could be consumed as part of the general diet. Data from the National Diet and Nutrition Survey (NDNS) (Bates *et al*., 2014, 2016, 2020; Roberts *et al*., 2018) on acute herbal and fruit tea consumption and honey among women of childbearing age (16-49 years) may provide an indicator of *Echinacea* intake from these foods during pregnancy. The acute consumption scenario is considered because *Echinacea* products are likely to be consumed for a short period of time during an episode of cold/flu during pregnancy. The NDNS does not provide data for pregnant or lactating women, so while data is based on women of childbearing

age, this may not necessarily be representative of the maternal diet. It is also worth noting that some of the *Echinacea* containing tea products advise pregnant or lactating women to consult a healthcare professional prior to using the product. The *Echinacea*-containing honey states that it is suitable for pregnant or breastfeeding women, whilst the lozenges contain no warnings. Like tablets and capsules, lozenges are solid dosage forms, but they are specifically designed to dissolve or disintegrate slowly in the mouth and are formulated with a flavoured or sweetened base.

85. The NDNS data indicate that women of childbearing age consume a mean of 520 mL/person/day or 1,500 mL/person/day at the 97.5th percentile of herbal and fruit tea at the acute consumption level (Table 3). The consumption of herbal and fruit tea has been used as a proxy for the consumption of *Echinacea* tea. Information from *Echinacea* tea products available suggests preparing the teacup with 227-250 mL hot water and consumption recommendations vary between 2-6 cups per day (Appendix B, Table 7). Based on the *Echinacea* content of the tea products, (Table 7, Appendix B) that would provide 144 - 1005 mg *Echinacea* per cup of tea, assuming 100% extraction efficiency. Taking the NDNS data for the consumption of herbal and fruit teas into consideration and the assumption that a cup of *Echinacea* tea will be prepared with 250 mL water, this would equate to the consumption of 6 cups of *Echinacea* tea per day at the 97.5th percentile by women of childbearing age. This corresponds to an estimated acute exposure of 864 to 6,030 mg of *Echinacea* per day at the 97.5th percentile, resulting from the consumption of *Echinacea* tea.

Table 3: Acute consumption of herbal and fruit tea (as consumed), as a proxy for *Echinacea* tea consumption (without recipes)

Consumers (n)^	**Mean (mL/person /day)**	**97.5th percentile (mL/person /day)**	**Mean (mL/kg/ bw/day)**	**97.5th percentile (mL/kg bw/day)**
364	520	1,500	8.0	23

*Rounded to 2 significant figures.

^Based on women of childbearing age (16-49 years).

86. The NDNS data on honey consumption (Table 4) suggests that women of childbearing age have a mean acute consumption of honey of 15 g/person/day honey or 48 g/person/day at the 97.5th percentile. *Echinacea* honey products contain 0.4-2.1 mg *Echinacea* per 1 g honey (Appendix B, Table 7). This corresponds to an estimated acute exposure of 19 to 101 mg of *Echinacea* per day at the 97.5th percentile, resulting from the consumption of *Echinacea* honey.

Table 4: Acute consumption of honey as a proxy for *Echinacea* honey consumption (without recipes)

Consumers (n)^	**Mean (g/person /day)**	**97.5th percentile (g/person /day)**	**Mean (g/kg/ bw/day)**	**97.5th percentile (g/kg bw/day)**
293	15	48	0.23	0.75

*Rounded to 2 significant figures.

^Based on women of childbearing age (16-49 years).

87. *Echinacea* supplements available online include solid dosage forms (tablets and capsules; Appendix B, Table 8) and oral liquids (solutions and tinctures; Appendix B, Table 9). Most of these supplements advise consulting a healthcare provider prior to using them during pregnancy/breastfeeding or state that they are not suitable for use during these periods. In addition, some of the supplements recommend short-term use only (5 days to several weeks). For products with herbal blends or unclear directions, the daily *Echinacea* dose is difficult to determine. Where extracts are specified, tablets/capsules provide 130–700 mg dry herb extract (equivalent to 1,300–7,000 mg herb). Products with dried plant parts contain 400–3,600 mg herb or 500–3,200 mg root. Fewer oral liquid products were found, and some lacked clear composition or usage instructions. Available liquids deliver 500–1,500 mg herb extract or 600–3,000 mg dried herb daily.

88. The *Echinacea* products for oral use with THR from the MHRA include tablets, capsules, oral solutions, tinctures and oromucosal spray (Appendix B, Table 13). The most common are tablets and capsules containing dry extract of *E. purpurea* root, with daily doses of 143–429 mg (equivalent to 858–3,000 mg root).

Preparations from dried pressed juice of *E. purpurea* herb provide 176–352 mg daily (equivalent to 3.5–9.8 g fresh herb). A comparison between the THR products and the EMA monographs in terms of species used, preparations and doses can be found in Table 14, Appendix B. There is no evidence to suggest that THR products and *Echinacea* food supplements are taken together during pregnancy, and the assumption is that this is unlikely, especially since the THR products advise against use in pregnancy in their patient information leaflets. In addition, the regulation of THR products is a remit of the MHRA and the *Echinacea* exposure from licensed herbal *Echinacea* products is therefore not considered in the combined exposure scenarios.

89. Pregnant women may consume *Echinacea* through various sources, including herbal teas, honey, lozenges, and food supplements such as tablets, capsules, and oral liquids. The FSA's Exposure Team estimated *Echinacea* intake during pregnancy under different worst-case scenarios, combining these products. The combined exposure values (Tables 8-11 Appendix B) are based on recommended doses from product labels for food supplements (tablets, capsules, lozenges and oral liquids) and estimated intakes from NDNS consumption data for herbal tea, honey and lozenges. Table 5 presents acute exposure estimates from individual products, while Table 6 shows minimum and maximum combined exposures. Results indicate that combined use of foods and food supplements could reach *Echinacea* (as dried herb/root) intakes of up to 13,000 mg/day.

Table 5: Estimated minimum and maximum acute exposures to Echinacea (as dried root/herb) from individual Echinacea containing products

Echinacea containing food/food supplement	**Estimated exposure to *Echinacea* (mg/day)**
Tea	860 – 6,000
Honey	19 - 100
Lozenges	40
Tablets/capsules	400 – 3,600

Oral liquids	600 – 3,000

*Rounded to 2 significant figures.

Table 6: Estimated minimum and maximum acute exposures to Echinacea (as dried root/herb) based on combined consumption of Echinacea products

Number of *Echinacea* products consumed per day	**Minimum estimated exposure to *Echinacea* (mg/day)**	**Maximum estimated exposure to *Echinacea* (mg/day)**
2	60	9,600
3	460	13,000
4-5	1,100	13,000

*Rounded to 2 significant figures.

Risk Characterisation

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8. Annex A to TOX/2026/11 - Toxicity Studies
9. Annex A to TOX/2026/11 - Adverse effects in humans
10. Annex A to TOX/2026/11 - Duration of use
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90. There are several layers of uncertainty regarding the safety of Echinacea supplements consumption during pregnancy and lactation. There are three different Echinacea species in medicinal use, E. purpurea, E. pallida and E. angustifolia, with different parts of the plant (root, herb, flower or whole plant) utilised and different methods of extraction used (powdered plant parts, dry and liquid extracts, pressed and dried pressed juice). The composition of bioactive components varies depending on the preparation and there is currently no consensus on how the Echinacea preparations should be standardised. The impact of differences in composition on the toxicological potential between the available products is therefore unknown. In addition, some of the supplements and food products do not state the Echinacea species, part of plant or preparation type, rendering comparison between products challenging.

91. Echinacea products are available as foods (Appendix B, Table 7), supplements (Appendix B, Tables 8-9) and as traditional herbal medicinal products with THR from the MHRA (Appendix B, Table 13). Echinacea food supplements and products with THR share some similarities such as the species (predominantly E. purpurea and E. angustifolia) and use of dosage forms such as capsules, tablets and tinctures. The THR products are typically single-herb preparations made from pressed juice or extracts of fresh or dried herb/root. They have defined drug-extract ratios (DER), and both the extract quantity and corresponding herb equivalent are clearly stated.

92. In contrast, Echinacea food supplements are often blended with additional supplements (e.g goldenseal, garlic, multivitamins) and employ mixed use of aerial parts, roots or whole plant or extracts with variable DER. It is therefore challenging to compare THR products, for which established monographs exist and an assessment of the quality and safety has been performed by regulatory agencies, to the food supplements which have greater variability in the formulation with key information on the species and preparation type and dose sometimes missing from the label.

93. The daily doses from Echinacea tablets/capsules food supplements, where available, range from 400 to 3,600 mg (dried herb) and 500 to 3,200 mg (dried root). These doses are comparable to the daily doses of THR products based on dry E. purpurea root extract (143-429 mg dry root extract equivalent to 858 – 3,000 mg root). Many of the Echinacea food supplements carry labels warning against the use of the product during pregnancy and lactation.

94. The EMA and the MHRA explicitly advise against the use of Echinacea-containing medicinal products during pregnancy and lactation due to the absence of high-quality, guideline-compliant reproductive and developmental toxicity studies and the limited, insufficient human data available to support safety in these populations. EMA monographs state that, in the absence of robust preclinical evidence and adequately powered human studies, Echinacea medicinal products should not be used during pregnancy or breastfeeding. Likewise, MHRA-authorised THR products carry mandatory warnings against use in pregnancy and lactation. These recommendations relate specifically to medicinal Echinacea products, for which the composition, dose and quality specifications are defined as part of their product license. In contrast, for many Echinacea food supplements the species, preparation type and dose are not consistently reported, making their composition and exposure levels more uncertain.

95. The Echinacea products with THR recommend a duration of use no longer than 10 days. This is in line with the EMA monographs on E. purpurea, E. angustifolia and E. pallida. Some, but not all, commercially available food supplements also advise limited use, typically between 5 days and 2 weeks. In contrast, Echinacea has been used in a clinical study for durations up to 6 months at doses of 1,800 mg/day with minimal side effects such as nausea and diarrhoea , but pregnancy was an explicit exclusion criteria for that trial (Vonau et al., 2001). Doses of 2,400-4,000 mg daily were also well tolerated in a 4 month long study with 755 participants (Jawad et al., 2012). Given the indications for Echinacea use and the warnings on most products to avoid prolonged use,

Echinacea products are likely to be consumed short term for the treatment and relief of common cold symptoms during pregnancy.

96. The estimated exposures to Echinacea by the FSA Exposure assessment team (EAT) range between 400 – 3,600 mg from food supplements (oral liquids, tablets, capsules), 19-100 mg from honey and 860 – 6,000 mg from tea products. If a combination of food and food supplement products are taken, exposure levels can reach up to 13,000 mg/day. Echinacea doses used in clinical studies vary between 100-4,000 mg/day extract and 6,200-10,000 mg/day pressed juice with duration from 5 days to 4 months, with E. purpurea and E. angustifolia being the most commonly used.

97. It is important to note that Echinacea preparations are complex mixtures, and their assessment presents common challenges associated with mixture toxicity. These include batch-to-batch variability, uncertainties in extraction efficiency (particularly for tea preparations), and variability in the bioavailability of active constituents. A further caveat is that the exposures estimated by the EAT team are based on dried Echinacea root/herb rather than extracts/pressed juice as many of the supplements and food products either list the Echinacea content as dried plant parts or do not specify the nature of the preparation. Thus, a direct comparison is challenging as generally extracts are more concentrated and potent than the dried plant equivalents.

98. There is additional uncertainty surrounding the health risk posed by potential contaminants in Echinacea preparations. There are very few studies looking at the presence of contaminants such as heavy metals, fungi, bacteria and mycotoxins in Echinacea products. Alternaria alternata, Aspergillus spp., Fusarium spp., Phoma spp., yeasts and mycotoxins have been detected in Echinacea herbal supplements available on the Polish market (Tournas, 2009). Whilst cadmium, arsenic and lead have been detected in commercial Echinacea products, their levels have been considerably lower than the limits set by WHO and they were not considered to pose a health risk to the public (Filipiak-Szok et al., 2015; Raman et al., 2004).

99. No evidence of genotoxicity has been observed with E. purpurea and E. angustifolia herbal medicinal preparations in in vitro bacterial reverse mutation assays, in vitro chromosomal aberration tests as well as in vivo micronucleus test conducted by several OECD guideline conforming studies. The animal data from studies investigating the acute, subacute and sub-chronic toxicity of Echinacea suggest that overall Echinacea has low toxicity and is well tolerated. Upon reviewing the data from human studies on E. purpurea, EMA (2014) concluded

that oral preparations are well tolerated and have an acceptable safety profile with mild, transient and reversible adverse effects, with gastrointestinal disturbances and allergic skin reactions being the most commonly reported adverse effects. However, the EMA does not recommend the use of Echinacea medicinal preparations during pregnancy and lactation due to the lack of guideline-conforming preclinical data on reproductive and developmental toxicity.

100. Case reports and pharmacovigilance data suggested that Echinacea may cause severe allergic reactions, including anaphylaxis, especially in atopic individuals (Mullins & Heddle, 2002; EMA, 2014). Isolated reports link Echinacea to autoimmune conditions such erythema nodosum, hyperoesinophilia, leucopenia, thrombocytopenia and severe acute cholestatic autoimmune hepatitis. Upon reviewing these case reports, EMA deemed that the causality of adverse events in pharmacovigilance cases concerning autoimmune diseases is not known or inconclusive, but association with autoimmune diseases cannot be excluded (EMA, 2014). EMA also stated that based on the presumption that Echinacea has immunomodulatory properties, it is not recommended in progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system (EMA, 2014). The COT agreed that individuals with atopic disease or autoimmune disorders will be at higher risk than the general population from exposure to Echinacea products and this should be taken into account for in the risk assessment.

101. Studies have demonstrated that Echinacea and its extracts can inhibit recombinant human cytochrome P450 (CYP) enzymes 3A4, 2E1, 1A2, 2C19 and 2C9 enzymes in vitro to various degrees (Husain et al., 2023; Modarai et al., 2010; Raner et al., 2007; Yale and Glurich, 2005). The total alkylamide content of the Echinacea preparations has been positively associated with its ability to inhibit the CYP enzymes, in particular CYP3A4 (Modarai et al., 2010) and CYP2E1 (Raner et al., 2007). In humans, short-term use (1,600 mg/day E. purpurea for 8 days) inhibited intestinal CYP3A4 and CYP1A2. CYP1A2 inhibition was considered clinically relevant for drugs like theophylline (Gorski, 2004), although no interaction with theophylline has been reported. Longer-term E. purpurea use (1,600 mg/day for 28 days) showed no significant CYP changes (Gurley, 2004). Overall, Echinacea has the potential to interact with medications, but clinical evidence remains limited.

102. The COT agreed there was a lack of high-quality available data on the reproductive end points from both animal and human studies. None of the animal

studies available on the reproductive and developmental effects of Echinacea conform to the OECD guidelines. A potential data gap identified by the Committee was the absence of studies looking at the placenta and the maintenance of pregnancy. It was highlighted that identifying these data gaps is particularly important given the recommended short-term use of Echinacea leading to a transient exposure window during the different parts of the reproductive and developmental cycle.

103. Two mice studies (Chow et al., 2006 and Barcz et al., 2007) investigated the effects of Echinacea during pregnancy with one focused on spontaneous abortions and the other on foetal angiogenesis. Chow et al. (2006) reported increased foetal loss in the Echinacea treated mice by 12-14 days of gestation and warned against the consumption of Echinacea in the early stages of pregnancy. Barcz et al. (2007) reported a significant decrease in angiogenic factors VEGF and bFGF with the three different Echinacea preparations tested but observed conflicting effects on angiogenic activity: one preparation increased activity, another decreased it, and the third showed no effect. Barcz et al. (2007) concluded that Echinacea may influence foetal angiogenesis and recommended avoiding its use during pregnancy as a precaution.

104. The COT highlighted that small numbers of animals were used in both mice studies with only one dose of Echinacea tested. In addition, the COT Members were not convinced by the conclusion reached by Chow et al. (2006) stating that Echinacea could lead to miscarriages in early pregnancy as the study had used a DBA mouse strain with small litter size and the range/standard deviation for the foetal loss results were not provided.

105. No interventional clinical trials exist on Echinacea use during pregnancy or lactation (EMA, 2014). Limited human data from observational studies (Gallo et al., 2000; Heitmann et al., 2016) and surveys (Cuzzolin et al., 2010; Nordeng et al., 2011) show no adverse maternal or infant effects specifically linked to Echinacea. Both observational studies (Gallo et al., 2000; Heitmann et al., 2016) reported no significant differences in malformations, birth weight, or pregnancy outcomes between exposed and control groups. The COT commented that the sample size in the study by Gallo et al. (2000) would not give sufficient statistical power to detect the birth defects and malformations studied. The COT also highlighted that the limited human studies on the use of Echinacea during pregnancy focus on observations that can be detected at birth and did not consider any longer-term effects such as epigenetic changes.

106. The human studies suggest that Echinacea is consumed during pregnancy for similar indications as in the general population including the treatment and prevention of cold and flu and respiratory tract infections such as sinusitis, tonsilitis, cough, bronchitis and pneumonia. The COT Members highlighted that the Holst et al. (2011) study reporting 4.3% of women using Echinacea during pregnancy was conducted between the months of November and February, which could lead to an overestimation due to increased incidence of cold and flu infections during the winter months. The COT also noted that the transient exposure makes it difficult to determine the percentage of women using Echinacea during the different stages of pregnancy and what the implications of extrapolating from different types of studies are.

107. Overall, the COT agreed that the human studies available lack information about the specific Echinacea species, plant part, type of preparation used, administered dose, the duration of intake and the trimester during which Echinacea was used. It is therefore not possible to directly compare doses used during pregnancy in ‘real life’ situations to exposures estimated by the FSA EAT team. In addition, the COT agreed that the point of departure for Echinacea to be used in risk assessments was difficult to derive due to complexity in terms of preparations, extracts, doses and lack of sufficient, high-quality data to determine clear safety risks.

Annex A to TOX/2026/11

Conclusions

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7. Annex A to TOX/2026/11 - Reproductive and developmental studies on Echinacea
8. Annex A to TOX/2026/11 - Toxicity Studies
9. Annex A to TOX/2026/11 - Adverse effects in humans
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108. Three *Echinacea* species – *E. purpurea*, *E. angustifolia* and *E. pallida* have been used medicinally to relieve the symptoms and shorten the duration of cold and flu infections. *Echinacea* preparations can be made from the dried roots of all three species, the fresh or dried aerial parts and the pressed juice from *E. purpurea*. Ethanolic extracts are also often used in many *Echinacea* products. The effects of *Echinacea* are due to the combination of bioactive metabolites including alkylamides, caffeic acid derivatives and polysaccharides. The composition of these compounds varies across the species, the plant parts, season, growing conditions and extraction methods used.

109 There is evidence from *in vitro* and *in vivo* studies that *Echinacea* preparations can inhibit viral entry and modulate immune responses following infection. Herbal products containing *E. purpurea*, *E. angustifolia* and *E. pallida* have herbal medicinal licenses in EU/EEA member states and THR license from the MHRA based on traditional use for the relief of common cold symptoms in adults and children over 12 years of age. Regulatory authorities, including the EMA and MHRA, do not recommend the use of *Echinacea* containing medicinal products during pregnancy or lactation due to the absence of high-quality, guideline-conforming reproductive and developmental toxicity studies and the limited human evidence available. THR licensed *Echinacea* products in the UK also carry warnings advising against use in these populations. Nevertheless, survey data indicate that up to 10% of pregnant women may use *Echinacea* for the treatment or prevention of cold and flu symptoms or for immune support.

110. In addition to products with a THR license, there is a range of foods and food supplements containing *Echinacea* and its extracts. The most common food supplements are tablets and capsules, and the majority of these products carry a warning against their use in pregnancy/lactation and a recommendation for short term use only. There are also food products such as tea and honey which contain *Echinacea.* Whilst products with THR are acknowledged in this paper, the focus in the conducted exposure assessment has been the consumption of *Echinacea* foods and food supplements.

111. The *in vivo* toxicological studies on *Echinacea* suggested that it has low toxicity. Clinical studies reported that *Echinacea* products are well tolerated with minor and reversible side effects including gastrointestinal disturbances and allergic skin reactions. There are isolated case reports of *Echinacea* causing erythema nodosum, hyperoesinophilia, leucopenia, thrombocytopenia and hepatotoxicity, but causality has not been confirmed. Pharmacovigilance cases and follow up investigation of selected patients also suggested that *Echinacea* can trigger allergic reactions, as serious as anaphylaxis in some cases, in patients with pre-existing atopic diseases. EMA (2014) recommends *Echinacea* preparations should be used with caution in patients with asthma or history of atopy. Due to its potential for immune system modulation, *Echinacea* is also not recommended for people with autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system.

112. There is an uncertainty around the potential of *Echinacea* to interact with prescription medicines during pregnancy. *In vitro* and *in vivo* studies demonstrated that *Echinacea* could affect the activity of CYP enzymes leading to inhibition of CYP1A2 and CYP3A4. However, the clinical relevance of these *in vitro* and *in vivo* studies is unknown as there are limited number of human studies investigating the interactions of *Echinacea* with over the counter or prescription medicines.

113. Contaminants such as heavy metals, fungi, bacteria, mycotoxins and pesticides are sometimes found in herbal preparations. There is an uncertainty of how much risk the potential contaminants in *Echinacea* preparations pose to pregnant consumers due to lack of research. Whilst studies have reported that cadmium and lead levels detected in *Echinacea* preparations have been lower than the WHO limits, the presence of fungal contaminants and mycotoxins found in some *Echinacea* products can pose an additional risk during pregnancy.

114. There is a lot of uncertainty around the safety of using *Echinacea* products during pregnancy or lactation due to limited data from *in vitro*, *in vivo*

and clinical studies. *In vitro* and *in vivo* OECD guideline conforming studies suggested that *Echinacea* is not genotoxic. There are two studies in mice, one in pigs and two studies in rabbits looking at the effects of *Echinacea* supplementation during pregnancy. Whilst the two mice studies highlighted potential increase in foetal loss and altered angiogenesis with *Echinacea*, the sample sizes were small and some of the results reported on foetal angiogenesis were conflicting. The pig and rabbit studies did not report any significant differences in relation to birth weight, pregnancy outcomes and frequency of malformations between *Echinacea* and control groups. There are human observational studies describing the effects of *Echinacea* on pregnancy outcomes and they did not highlight any adverse effects associated with gestational use of *Echinacea*. These studies rely on self-reported use of *Echinacea* during pregnancy and the dose, preparation or duration of use were not specified.

115. The doses used in clinical studies on the efficacy of *Echinacea* are comparable to the estimated exposures to *Echinacea* in women of child-bearing age, calculated by the FSA Exposure Assessment Team. *Echinacea* was well-tolerated in these clinical studies, but they did not include pregnant or lactating women. In addition, an exact comparison between different *Echinacea* products is challenging due to products containing different combinations of the three medicinally used species, their dried plant parts and extracts. Some food products such as tea and honey often lack information on the exact species, plant parts or extracts used.

116. Overall, Members emphasised that the available information is insufficient to support a robust risk assessment or the derivation of any health-based guidance values. However, the Committee did not identify any reason to expect adverse effects in humans from the current levels of exposure of *Echinacea* as part of the maternal diet.

Annex A to TOX/2026/11

List of Abbreviations

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2. Annex A to TOX/2026/11 - Existing authorisations for Echinacea products in the UK
3. Annex A to TOX/2026/11 - European Medicines Agency (EMA) assessment reports and conclusions
4. Annex A to TOX/2026/11 - Health-based guidance values (HBGVs)
5. Annex A to TOX/2026/11 - Toxicokinetics
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ACAH	Acute cholestatic autoimmune hepatitis
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reactions
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve

bFGF	Basic fibroblast growth factor
BMDCs	Bone marrow derived dendritic cells
bw	Body weight
CAM	Complementary and alternative medicines
CFS	Chronic fatigue syndrome
CFU	Colony forming units
CI	Confidence intervals
CYP	Cytochrome P450
DER	Drug extract ratio
DTAI	Dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides
EFSA	European Food Standards Agency
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicine Agency
FCV	Feline calicivirus
FDA	Food and drug administration
GLP	Good laboratory practice

GHS	Globally Harmonized Classification System
HBGV	Health-based guidance values
HMR	Human Medicines Regulation
HMPC	Committee on Herbal Medicinal Products
HPLC	High performance liquid chromatography
HPRT	Hypoxanthine phosphoribosyltransferase
HSV	Herpes simplex virus
ICP-MS	Inductively-coupled plasma mass spectrometer
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
INF	Inteferon
IV	Intravenous
LDH	Lactate dehydrogenase
LU	Lytic units
MAPK	Mitogen-activated protein kinase

MDCK	Madin-Darby canine kidney cells
MHRA	Medicines and Healthcare Products Regulatory Agency
MN	Micronuclei
MNPCE	Micronucleated polychromatic erythrocytes
NHANES	National Health and Nutrition Examination Survey
NCE	Normochromatic erythrocytes
NDNS	National Diet and Nutrition Survey
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK cells	Natural killer cells
OECD	Organisation for Economic Co-operation and Development
PBMC	Peripheral blood mononuclear cells
PCE	Polychromatic erythrocytes
PFU	Plaque-forming unit
P-gp	P glycoprotein
PMN	Polymorphonuclear leukocytes
PNG	Polymorphonuclear neutrophil granulocytes

RBCs	Red blood cells
RET	Reticulocytes
RPMI	Roswell Park Memorial Institute
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SHE	Syrian hamster embryo cells
SMA	Smooth muscle antibodies
STP	Skin prick testing
TGF-β1	Transforming growth factor beta
THR	Traditional herbal registration
TNF	Tumour necrosis factor
TTP	Thrombotic thrombocytopenic purpura
UKTIS	UK Teratology Information Service
VEGF	Vascular endothelial growth factor
WBC	White blood count
WHO	World Health Organization

References

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