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TOX/2026/11

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

Second Draft Statement on the potential health risks of Echinacea in the maternal diet

Introduction

1. As part of the Scientific Advisory Committee on Nutrition's (SACN) current programme of work on the potential risks from the maternal diet, the COT reviewed a scoping paper ([TOX/2020/51](#)) on commonly used herbal supplements during pregnancy. *Echinacea*, marketed for immune support and for the prevention or treatment of cold and flu-like symptoms, was among the supplements considered.
2. In December 2025, the Committee reviewed a first draft statement on the effects of *Echinacea* in the maternal diet ([TOX/2025/45](#)). Members were broadly satisfied with the risk characterisation and overall conclusions but recommended re-wording the final concluding sentence regarding the risk of *Echinacea* consumption during pregnancy. Members also requested that the risk characterisation section acknowledges that *Echinacea* preparations are complex mixtures, and that their risk assessment involves common challenges associated with mixture toxicity.
3. The Committee also commented on the organisation of the reproductive and developmental data, as well as the sequence in which the reproductive and developmental effects of *Echinacea* and the general adverse effects in humans were presented. It was suggested that the section on the reproductive and developmental effects of *Echinacea* should be discussed earlier in the statement after the toxicokinetics section in order to keep the maternal effects the focus of the

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statement. Members also advised that the colour-coding in Table 1 summarising the reproductive and developmental studies should be replaced with the terms insufficient, limited, and adequate more accurately reflect study quality and data sufficiency.

4. Further revisions were made to the statement to address Members' comments on the genotoxicity section, including clarification on the OECD compliance of the studies considered.

5. A second draft statement (Annex A) has been prepared, incorporating Members' comments and suggested revisions.

Questions for the Committee

The Committee are asked to consider the following questions:

- a) Is the Committee satisfied with the layout and structure of the second draft statement following the revisions made?
- b) Does the Committee have any further comments on the second draft statement?
- c) Given that herbal medicinal *Echinacea* products have defined compositions and regulatory oversight, while food supplements do not, and that regulatory authorities such as the EMA and MHRA do not recommend the use of medicinal *Echinacea* products during pregnancy or lactation due to insufficient safety data, does the Committee agree with the overall conclusion of the statement?

Secretariat

March 2026

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TOX/2026/11 Annex A

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

First Draft Statement on the potential health risks of *Echinacea* in the maternal diet

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

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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

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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* preparations.

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Existing authorisations for Echinacea products in the UK

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).

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European Medicines Agency (EMA) assessment reports and conclusions

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 Pharmacopoeia 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,

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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 ketoalkenyne

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(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.

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Health-based guidance values (HBGVs)

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

Toxicokinetics

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 C_{max} 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

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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*.

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Effects on cytochrome P450 and P-glycoprotein

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

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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.

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Reproductive and developmental studies on *Echinacea*

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.

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34. Barcz *et al.* (2007) aimed to investigate whether pharmaceuticals containing desiccated 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.

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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,

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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 (Kovitvadhii *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

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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

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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

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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.

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

Study reference	Study type	<i>Echinacea</i> preparation and dose	Stage A (pre-mating to conception)	Stage B (conception to implantation)	Stage C (implantation to parturition - pregnancy)	Stage D (post-partum including lactation)
Chow <i>et al.</i> 2006	Animal study (DBA/2 mice)	<i>E. purpurea</i> extract 0.45 mg/kg bw/day (dose per body weight)	Insufficient	Limited	Limited	Insufficient
Barcz <i>et al.</i> 2007	Animal study (Balb/c mice)	<i>E. purpurea</i> extract 0.6 mg/day	Insufficient	Limited	Limited	Insufficient
Maass <i>et al.</i> , 2005)	Animal study (pigs)	<i>E. purpurea</i> dried cobs 0.5-3.6%	Insufficient	Insufficient	Limited	Adequate
Dabbou <i>et al.</i> , 2016	Animal study (rabbits)	<i>E. pallida</i> 3 g/kg	Insufficient	Adequate	Adequate	Adequate
Kovitvadhi <i>et al.</i> , 2016	Animal study (rabbits)	<i>E. pallida</i> 3 g/kg	Insufficient	Insufficient	Insufficient	Adequate
Gallo <i>et al.</i> , 2000	Human prospective controlled study	<i>E. purpurea</i> and <i>E. angustifolia</i> 250- 1000 mg/day	Insufficient	Insufficient	Limited	Insufficient
Heitmann <i>et al.</i> , 2016	Human prospective cohort study	Not specified	Insufficient	Insufficient	Limited	Insufficient
Cuzzolin <i>et al.</i> , 2010	Human cross-sectional study	Not specified	Insufficient	Insufficient	Limited	Insufficient
Nordeng <i>et al.</i> , 2011	Human cross-sectional study	Not specified	Insufficient	Insufficient	Limited	Insufficient
Matthias <i>et al.</i> , 2008	Human case report	Four tablets each containing <i>E.</i>	Insufficient	Insufficient	Insufficient	Limited

		<i>purpurea</i> 675 mg and <i>E. angustifolia</i> 600 mg				
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* The terms insufficient, limited, and adequate indicate the degree to which the study addresses and provides relevant data for the specific maternal life-history stage.

Toxicity Studies

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-dimethylthiazol-2-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

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both cancer cell lines, with calculated IC₅₀ 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 LD₅₀ 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

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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

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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

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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

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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. Mengers *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

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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 *in 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

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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-aminoanthracene, 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

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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

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

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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

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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,

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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

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

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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

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

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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 $\mu\text{g/mL}$, 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.

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Table 2: Summary of the immunomodulatory effects of *Echinacea*

<i>Echinacea</i> preparation	Concentration or dose	Test system	Summary of immune system effects	Reference
Fresh and dried juice from EchinaFresh (<i>E. purpurea</i>) standardized for a content of 2.4% soluble β -1,2-D-fructofuranosides.	0.05-10 μ g/mL fresh juice and 0.01-10 μ g/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 <i>Echinacea</i> .	Burger <i>et al.</i> , 1997
<i>E. purpurea</i> raw herb and root powders subjected to simulated digestion protocol in simulated gastric fluid.	5 – 320 μ g/mL	RAW267.7 murine macrophages	Dose dependent induction of TNF- α , NO, IL-1 α , IL-1 β , and IL-6 with <i>Echinacea</i> treatment comparable to the results observed with the LPS positive control.	Rinninger <i>et al.</i> , 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 μ L <i>via</i> oral gavage	Male Sprague-Dawley rats	<i>Echinacea</i> 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 <i>et al.</i> , 2002
Commercially available <i>E. purpurea</i>	400 μ g/mL	Bone marrow-derived dendritic cells (BMDCs)	<i>Echinacea</i> treatment significantly increased percentage of CD40, CD80, CD83 and CD86	Li <i>et al.</i> , 2017

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<p>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%).</p>		<p>derived from femur and tibia of 6–8-week-old female C57BL/6 mice.</p>	<p>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 <i>Echinacea</i> treatment, similar to results observed with LPS control.</p>	
<p>Dried, ground preparations of fresh <i>E. purpurea</i> herb homogenized, filtered and used fresh the same day.</p>	<p>0.001 to 1000 pg/mL</p>	<p>Human peripheral blood mononuclear cells (PBMC) from healthy patients or patients with chronic fatigue syndrome (CFS) or acquired immunodeficiency syndrome (AIDS).</p>	<p>Significant increase in the NK cell activity from healthy patients and those with CFS and AIDS was observed following <i>Echinacea</i> 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 <i>E. purpurea</i> treatment.</p>	<p>See <i>et al.</i>, 1997</p>
<p><i>E. purpurea</i> dissolved in water and filtered to prepare a water soluble extract.</p>	<p>Concentrations up to 10 μg/mL</p>	<p>Human peripheral blood mononuclear cells (PBMC)</p>	<p>Increase in the NK-mediated cytotoxic activity was observed with <i>E. purpurea</i> treatment in a concentration dependent manner. <i>Echinacea</i> 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.</p>	<p>Gan <i>et al.</i>, 2003</p>

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<p>Ground <i>E. purpurea</i> aerial parts and freeze dried into a powder. The preparation contained cichoric and caftaric acids, as well as cynarin, but not alkylamide.</p>	<p>Concentrations of up to 250 µg/mL</p>	<p>Human T-cell line Jurkat E6-1</p>	<p><i>E. purpurea</i> induced a dose-dependent increase in IL-2 secretion and a five-fold rise of IFN-γ secretion by high-density T cells.</p>	<p>Fonseca <i>et al.</i>, 2014</p>
<p>Alcohol extracts of <i>Echinacea</i>. <i>E. purpurea</i> contained chicoric acid and caftaric acid, no echinacoside. <i>E. angustifolia</i> contained echinacoside, cynarin, chlorogenic acid. <i>E. pallida</i> contained echinacoside, chlorogenic acid and caftaric acid.</p>	<p>130 mg/kg bw/day by gavage</p>	<p>Eight-week-old male BALB/c mice</p>	<p>All three <i>Echinacea</i> species increased IFN-γ production in mitogen-stimulated splenocytes, suppressed IL-1β and TNF-α. In non-stimulated splenocytes, <i>E. purpurea</i> significantly increased IL-1β secretion. <i>E. purpurea</i> increased the percentage of CD49⁺ and CD19⁺ splenic cells, while <i>E. angustifolia</i> only increased CD49⁺; <i>E. pallida</i> had no effect on either. Only <i>E. pallida</i> significantly enhanced NK cell cytotoxicity.</p>	<p>Zhai <i>et al.</i>, 2007</p>

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Contaminants

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 $\mu\text{g/day}$, cadmium 0.004 – 0.967 $\mu\text{g/day}$, arsenic 0.027 – 0.908 $\mu\text{g/day}$, chromium 0.125-8.838 $\mu\text{g/day}$, and thallium 0.002 – 0.383 $\mu\text{g/day}$.

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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

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

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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)	97.5 th percentile (mL/person /day)	Mean (mL/kg/ bw/day)	97.5 th 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.

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

Consumers (n)^	Mean (g/person /day)	97.5 th percentile (g/person /day)	Mean (g/kg/ bw/day)	97.5 th 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

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

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*Rounded to 2 significant figures.

Risk Characterisation

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

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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-authorized 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

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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).

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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

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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

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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, tonsillitis, 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

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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.

Conclusions

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*. Ethanol 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

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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

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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.

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List of Abbreviations

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

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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- κ B	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

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STP	Skin prick testing
TGF- β 1	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

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TOX/2026/11 Appendix A

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

Discussion paper on the potential health effects of *Echinacea* in the maternal diet

Search methodology

1. The following electronic databases were searched for relevant articles published between 2014 and 2024: LitFetch (which includes material from PubMed, Scopus, Ebsco (Food Science Source) and Springer), Google and Google Scholar. The searches were conducted on various dates between 13th May 2024 and 24th May 2024.
2. The search terms used included 'echinacea' AND: ('pregnan*' OR 'maternal*' OR 'reproduction' OR 'gestation' OR 'lactation' OR 'preconception' OR 'development' OR 'tox*' OR 'safety' OR 'uses' OR 'consumption' OR 'indication' OR 'interaction').
3. The references from extracted papers were searched for citations not captured in the literature search. Only articles published in English were included, due to the linguistic abilities of the reviewer.
4. The UKTIS was also asked for information on any enquiries relating to maternal echinacea use and any reports of adverse effects in pregnant women or their newborn infants received from 1983 to June 2024. This included information relating to the type, dosage, duration, and timing of echinacea taken and any pregnancy outcomes captured through follow-up.

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TOX/2026/11 Appendix B

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

Statement on the potential health effects of *Echinacea* in the maternal diet

Table 7: Food products containing *Echinacea*.

Product name	Type	<i>Echinacea</i> species and plant part	Composition	Directions for use	Daily dose of <i>Echinacea</i> (mg)	Additional information/warnings
Pukka Herbs Elderberry and Echinacea Organic Herbal Tea	Tea bags	<i>Echinacea</i> (species not specified) herb	Ginger root, liquorice root, <i>Echinacea</i> herb (11%) , beetroot, aniseed, rosehip, peppermint leaf, orange peel, elderflower (5%), elderberry (4%), hibiscus, orange essential oil flavour, blackcurrant flavour.	Not specified	Not specified.	NA
Yogi Tea Echinacea Special Formula	Tea bags	Not specified	Cinnamon, <i>Echinacea</i> , ginger, fennel, rooibos, roasted chicory, carob, cardamom, basil, burdock root, black pepper, turmeric root, astragalus, vanilla beans.	Pour 250 ml of freshly boiled water over the teabag. Allow to infuse for 5 to 6 minutes - or longer for a stronger flavour.	Not specified.	NA

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<p>Yogi Tea, Echinacea Immune Support, Caffeine Free, 16 Tea Bags, 0.85 oz (24 g)</p>	<p>Tea bags</p>	<p><i>Echinacea purpurea</i> Plant part not specified</p>	<p>Each tea bag contains: 144 mg Echinacea purpurea, 47 mg Echinacea purpurea extract, 1,245 mg herb blend (rose hips, dried acerola juice, basil, cinnamon, ginger, cardamom, elderberries, black pepper, moringa, hibiscus, cocoa shells, liquorice, fennel).</p>	<p>Bring water to boiling and steep 7 minutes. For a stronger tea, use 2 tea bags. Drink 3-4 cups daily.</p>	<p>432 - 1,152 mg <i>Echinacea purpurea</i> and 141 - 376 mg <i>Echinacea purpurea</i> extract</p>	<p>Consult your healthcare provider prior to use if you are pregnant or nursing, taking any medication or if you have a medical condition.</p>
<p>Traditional Medicinals, Organic Echinacea Plus, Elderberry, Caffeine Free, 16 Wrapped Tea Bags, 0.85 oz (24 g)</p>	<p>Tea bags</p>	<p><i>Echinacea purpurea</i> herb</p>	<p>Each tea bag contains: 1005 mg Echinacea purpurea herb, 127.5 mg European elder flower, 1,245 mg herb blend (ginger rhizome, chamomile flower, yarrow flower, peppermint leaf, Echinacea purpurea root dry extract (2-8:1), European elder fruit dry concentrate).</p>	<p>Pour 8 oz (~227 mL) freshly boiled water over 1 tea bag. Cover & Steep for 10-15 min. Enjoy 5-6 cups throughout the day.</p>	<p>5,025 - 6,030 mg <i>Echinacea purpurea</i> herb</p>	<p>Do not use if you are pregnant or breastfeeding unless directed otherwise by your healthcare practitioner. Not recommended for use with children under 12 years of age.</p>
<p>Traditional Medicinals, Organic Immune Zoom®, Lemon Ginger Echinacea, Caffeine Free, 16 Wrapped Tea Bags, 1.13 oz (32 g)</p>	<p>Tea bags</p>	<p><i>Echinacea purpurea</i> root</p>	<p>2,000 mg herb blend (ginger rhizome, Echinacea purpurea herb, lemon myrtle leaf (<i>Backhousia citriodora</i>), lemon peel, liquorice root, peppermint leaf, Echinacea purpurea root dry extract (2-8:1), cardamom seed,</p>	<p>Pour 8 oz (~227 mL) freshly boiled water over 1 tea bag. Cover & Steep for 10-15 min. Enjoy 2 cups throughout the day.</p>	<p>Not specified.</p>	<p>Consult your healthcare practitioner prior to use if you are pregnant or breastfeeding; or if you have an autoimmune or other immune</p>

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			Organic liquorice root dry extract (6:1).			system disorder, or if you are taking immunosuppressants; or if you have liver or gallbladder disease. Not recommended for use with children under 12 years of age.
Superblends Defence 20 Tea Bags	Tea bags	<i>Echinacea</i> (species not specified) root	Green tea (26%), Ginger root (15%), White hibiscus, Cinnamon bark, Natural lemon Flavouring with other Natural Flavourings (10%), <i>Echinacea</i> root (9%) , Lemon peel (5%), Natural flavouring, Natural lime flavouring (4%), vitamin C (2%).	At least 1 cup a day.	Not specified.	NA
Frontier Co-op, Organic Cut & Sifted <i>Echinacea angustifolia</i> Root	Loose herb for tea	<i>Echinacea angustifolia</i> root	Half a teaspoon contains 1.1 g cut root.	To prepare as tea, pour 8 oz. (~227 mL) boiling water over 1/2 teaspoon of root. Cover and steep 20-30 minutes, strain and serve immediately.	Not specified.	If pregnant, nursing, suffering from any medical condition, or taking medication, consult a healthcare practitioner before use.
Frontier Co-op, Organic Elderberry <i>Echinacea</i>	Loose herb for tea	<i>Echinacea purpurea</i> herb and root	Elderberry, <i>Echinacea purpurea</i> herb , peppermint, yarrow, ginger, chamomile	Pour 8 oz. (227 mL) boiling water over 1 tablespoon of tea. Cover and steep 10-15	Not specified.	If pregnant, nursing, suffering from any medical condition, or taking

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Wellness Tea, 16 oz			flower, <i>Echinacea purpurea</i> root.	minutes, strain and serve immediately.		medication, consult a healthcare practitioner before use.
Frontier Co-op, Cut & Sifted Echinacea Purpurea Herb	Loose herb for tea	<i>Echinacea purpurea</i> herb	One teaspoon contains 820 mg <i>Echinacea purpurea</i> cut herb.	To prepare as a tea, pour 8 oz. (~227 mL) boiling water over 1 teaspoon of herb. Cover and steep 3-5 minutes, strain and serve immediately.	Not specified.	NA
Lemon & Ginger Vitamin Honey	Honey	Not specified.	1 teaspoon (7g) contains: 15 mg Echinacea , 3 mcg vitamin D3, 10mg vitamin C, 0.4 mcg vitamin B6, 0.4 mcg vitamin B12.	2 teaspoons into warm water.	Not specified.	This product is suitable for pregnant or breastfeeding women; however we'd always recommend that you consult with a health professional if you are unsure before making a purchase.
Orange Vitamin Honey	Honey	Not specified.	1 teaspoon contains: 15 mg Echinacea , 3 mcg vitamin D3, 10mg vitamin C, 0.4 mcg vitamin B6, 0.4 mcg vitamin B12.	2 teaspoons into warm water.	Not specified.	This product is suitable for pregnant or breastfeeding women, however we'd always recommend that you consult with a

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						health professional if you are unsure before making a purchase.
Wedderspoon Natural Manuka Honey and Ginger with Echinacea Drops (20 Drops per box)	Honey	Not specified.	Organic cane sugar, organic manuka honey (15.5%), organic brown rice syrup, ground ginger (0.6%), Echinacea (0.04%) .	Not specified.	Not specified.	NA
A.Vogel Echinacea Lozenges Extract of Freshly Harvested Echinacea Blend of Other Herbs Suitable for Vegetarians 30g	Lozenges	<i>Echinacea purpurea</i> herb and root extract	Each lozenge (2.2 g) contains: Glucose syrup, raw cane sugar, honey, herb extracts, fresh Echinacea purpurea extract (0.62%) , natural flavours, caramel colour, menthol, peppermint essential oil, citric acid.	As required.	Not specified.	NA
Honey Lemon Echinacea Soothe & Clear Drops 75g (Ricola)	Lozenges	<i>Echinacea</i> (species not specified) dry pressed juice	Sugar, glucose syrup, Fair Trade honey (5.1%), extract (0.5%) of Ricola's herb mixture, vitamin C, lemon juice concentrate, acid (citric acid, malic acid), natural flavourings, natural Echinacea aroma (Echinacea dry pressed juice) , mint oil, peppermint oil, menthol.	As required.	Not specified.	NA
Swanson, Zinc & C with Elderberry &	Lozenges	<i>Echinacea purpurea</i>	Each lozenge contains: 100 mg vitamin C, 25 mg	As a dietary supplement, dissolve	40 mg <i>Echinacea</i>	NA

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Echinacea, Orange & Lemon, 60 Lozenges		herb (aerial parts) powder	zinc, 20 mg Echinacea purpurea powder , 20 mg elderberry extract.	one lozenge in the mouth two times per day.	<i>purpurea</i> powdered herb.	
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Table 8: *Echinacea* food supplements (solid dosage forms).

Product name	Dosage form	<i>Echinacea</i> species and plant part	Composition	Directions for use	Daily dose <i>Echinacea</i> (mg)	Additional information
NOW Foods Echinacea 400 mg 100 Veg Capsules	Capsules	<i>Echinacea purpurea</i> root	400 mg root.	Take 2 capsules 1 to 4 times daily as needed. Continuous high level consumption of this product for more than 2 weeks of each month is not recommended.	800 - 3,200 mg root	For adults only. Consult physician if pregnant/nursing, taking medication, or have a medical condition.
Grape Tree Echinacea Root 500mg	Tablets	<i>Echinacea</i> (species not specified) root	500 mg root	1 tablet daily.	500 mg root	Linked to many health benefits including reduced inflammation, improved immunity and lower blood sugar levels.

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Swanson Echinacea, 400mg herbal supplement	Capsules	<i>Echinacea purpurea</i> herb (aerial parts)	400 mg herb.	1 capsule up to 3 times per day. Limit use to eight consecutive weeks. Use periodically for a few weeks at a time (for maintenance purposes).	400-1,200 mg herb	For adults only. Do not take this product if you are pregnant or nursing. Consult your healthcare provider before using this or any product if you are taking medication or have a medical condition, especially an autoimmune condition.
Echinacea, 1300 mg (per serving), 180 Vegetarian Capsules	Capsules	<i>Echinacea purpurea</i> herb (aerial parts)	65 mg herb extract (DER 10:1) equivalent to 650 mg herb.	Take 2 vegetarian capsules per day preferably with a meal.	130 mg herb extract equivalent to 1,300 mg herb	If you are pregnant, nursing, taking any medications or have any medical conditions, consult your doctor before use.
Life Extension, Echinacea Elite, 60 Vegetarian Capsules	Capsules	<i>Echinacea purpurea</i> herb and <i>Echinacea angustifolia</i> root	<i>Echinacea purpurea</i> (aerial parts) extract 125 mg [standardised to 4% phenolic compounds]. <i>Echinacea angustifolia</i> (root) extract 125 mg [standardised	Take 1 capsule twice daily.	250 mg <i>Echinacea purpurea</i> (aerial parts) extract and 250 mg <i>Echinacea angustifolia</i> (root) extract	Consult with your physician if you are undergoing treatment for a medical condition or if you are pregnant or lactating.

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			to 4% echinacosides].			
Specialist Herbal Supplies (SHS) Echinacea Capsules	Capsules	<i>Echinacea angustifolia</i>	325 mg. Preparation not specified.	1 capsule, 3 times a day, taken with food or a drink. If desired, up to four times this amount can safely be taken.	975-1,300 mg <i>Echinacea angustifolia</i>	If you are pregnant, breast-feeding, have a medical condition or are under medical supervision, please consult a doctor before use.
Nuke Nutrition Echinacea Tablets High Strength x180 - Immune Support Echinacea Herbal Supplements	Tablets	<i>Echinacea</i> . Species and part of plant not specified.	200 mg extract (DER 10:1) equivalent to 2,000 mg <i>Echinacea</i> .	Take 1 tablet with your first meal of the day.	200 mg extract equivalent to 2,000 mg <i>Echinacea</i>	Consult your physician if you are taking medication or are under medical supervision or if you are pregnant and breastfeeding.
Echinacea Extract Capsules 3500mg (High Strength) Echinacea purpurea	Capsules	<i>Echinacea purpurea</i> . Plant part not specified.	350 mg extract (DER 10:1) equivalent to 3,500 mg <i>Echinacea pupurea</i>	Take 1 capsule per day with water.	350 mg extract equivalent to 3,500 mg <i>Echinacea purpurea</i>	NA

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<p>Nature's Way, Echinacea Goldenseal, 450 mg, 100 Vegan Capsules</p>	<p>Capsules</p>	<p><i>Echinacea purpurea</i> herb (aerial parts) and <i>Echinacea angustifolia</i> root</p>	<p>450 mg <i>Echinacea 7</i> Herb Blend: <i>Echinacea purpurea</i> (stem, leaf, flower), Goldenseal (root), <i>Echinacea angustifolia</i> (root), Burdock (root), Gentian (root), Cayenne Pepper (fruit), Wood Betony (stem, leaf, flower).</p>	<p>Take 2 capsules twice daily, preferably with food.</p>	<p>1,800 mg <i>Echinacea 7</i> herb blend. Exact dose of <i>Echinacea</i> cannot be determined.</p>	<p>Do not use if you are pregnant, nursing, have stomach or duodenal ulcers, stomach irritation or inflammation. Not recommended for individuals with autoimmune conditions. If you have diabetes, or are taking any medications, consult a healthcare professional before use.</p>
<p>Nature's Way, Echinacea Purpurea Herb, 1,200 mg, 180 Vegan Capsules (400 mg per Capsule)</p>	<p>Capsules</p>	<p><i>Echinacea purpurea</i> herb (aerial parts)</p>	<p>400 mg herb</p>	<p>Adults take 3 capsules three times daily, preferably with food. Only take this supplement if they are suffering severe illness to stimulate the immune system and to not take for longer than 5 days.</p>	<p>3,600 mg herb</p>	<p>If pregnant, nursing, or taking any medications, consult a healthcare professional before use.</p>

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California Gold Nutrition, EuroHerbs, Echinacea Herb Extract, Euromed Quality, 80 mg, 180 Veggie Capsules	Capsules	<i>Echinacea purpurea</i> herb (aerial parts)	80 mg <i>Echinacea purpurea</i> (aerial parts) extract (DER 5:1) equivalent to 400 mg dried herb	Take 1 capsule daily, with food.	80 mg extract equivalent to 400 mg dried herb.	Pregnant or lactating women should consult with a physician, pharmacist, naturopath or other qualified healthcare professional prior to taking dietary supplements.
21st Century, Echinacea Complex, 250 mg, 60 Vegetarian Capsules (125 mg per Capsule)	Capsules	<i>Echinacea purpurea</i> herb and <i>Echinacea angustifolia</i> root	125 mg <i>Echinacea</i> blend (<i>Echinacea purpurea</i> herb extract and <i>Echinacea angustifolia</i> root powder)	Adults take two (2) capsules daily with any meal or as directed by a healthcare provider.	250 mg <i>Echinacea</i> blend (<i>Echinacea purpurea</i> herb extract & <i>Echinacea angustifolia</i> root powder)	Consult a healthcare provider prior to use if pregnant, nursing, on medications, have a medical condition or are planning a medical procedure.
Sundown Naturals, Whole Herb Echinacea, 400 mg, capsules	Capsules	<i>Echinacea purpurea</i> herb (aerial parts)	400 mg <i>Echinacea purpurea</i> herb	Take (1) capsule seven times daily, preferably with meals. Capsules may be opened and prepared as a tea.	2,800 mg herb	If you are pregnant, nursing, taking any medications or have any medical condition, consult your doctor before.
Gaia Herbs, Echinacea Goldenseal, 60 Vegan Liquid Phyto-Caps	Capsules	<i>Echinacea purpurea</i> root, aerial parts and seed and <i>Echinacea angustifolia</i> root	800 mg Proprietary Extract Blend: <i>Echinacea purpurea</i> root , Goldenseal (Hydrastis	Adults take 2 capsules 3 times daily between meals.	4,800 mg Proprietary Extract Blend. Exact dose of <i>Echinacea</i>	Not for use during pregnancy or lactation.

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			canadensis) root, <i>Echinacea angustifolia</i> root, <i>Echinacea purpurea</i> seed, St. John's Wort (<i>Hypericum perforatum</i>) aerial parts, <i>Echinacea purpurea</i> aerial parts.		cannot be determined.	
Specialist Herbal Supplies (Shs) Echinacea Compound	Capsules	<i>Echinacea angustifolia</i>	<i>Echinacea angustifolia</i> 92mg, Garlic 92mg, Myrrh 92mg, Wild Indigo 46mg. <i>Echinacea</i> preparation not specified.	1 capsule, 3 times a day, taken with food or a drink.	276 mg <i>Echinacea angustifolia</i>	Do not take alongside blood thinning drugs such as warfarin. Not to be used in pregnancy and breastfeeding or for children under 12 years old.

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Table 9: *Echinacea* food supplements (oral liquids).

Product name	Dosage form	<i>Echinacea</i> species and plant part	Composition	Directions for use	Daily dose <i>Echinacea</i> (mg)	Additional information
Nature's Way, Echinacea, 500 mg, 1 fl oz (30 mL)	Oral solution	<i>Echinacea purpurea</i> herb (aerial parts)	250 mg herb extract per 1 mL	Adults: Take 2 mL 3 times daily. Children ages 6-12 years of age: Take 1 mL 3 times daily. Intensive: Take 2 mL every 2 hours for first 48 hours. Then take 2 mL 3 times daily for next 8-9 days. May be added to foods/drinks.	Adults: 500-1,500 mg herb extract Children: 250-750 mg herb extract.	If pregnant, nursing, or taking any medications, consult a healthcare professional before use. Not recommended for individuals with auto-immune conditions.
Echinacea Single Herbal Tincture 150mL	Tincture	<i>Echinacea</i> (species not specified)	Dried herb to liquid ratio W/V 1:5 or fresh herb to liquid ratio W/V 1:3.	Dosage is normally between 1mL and 5 mL added to a little water up to three times a day.	3 - 15 mL herb extract daily equivalent to 600 -3,000 mg dried herb or 1,000 - 5,000 mg fresh herb	NA
Baldwins Echinacea (<i>angustifolia</i>) Herbal Tincture	Tincture	<i>Echinacea angustifolia</i>	Herb:Liquid 1:3	No guidance.	No guidance.	NA
Napiers the Herbalists Napier's Organic Echinacea Drops	Oral drops	<i>Echinacea purpurea</i> herb (aerial parts)	Not stated	Take 15-20 drops 2-3 times a day. 15 drops = 0.5 mL.	30 - 60 drops daily. Equivalent to	Not suitable for children under 12 years. Do not

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					1-2 mL solution.	take if pregnant or breastfeeding.
100% Organic Echinacea Tincture Viridian 50ml	Tincture	<i>Echinacea purpurea</i> whole plant	1 mL = 480 mg whole fresh plant.	Take 15 – 30 drops, 2-3 times daily in a little fruit juice or water. 15 drops = 0.5 mL.	31 - 60 drops daily. Equivalent to 1-2 mL solution or 480 - 960 mg fresh plant.	Not to be used during pregnancy or lactation unless recommended by a healthcare practitioner.
NOW Foods, Echinacea Extract, 2 fl oz (59 ml)	Oral solution	<i>Echinacea angustifolia</i> and <i>Echinacea purpurea</i> root	Root extract. 1.6 mL per 2 droppersfuls	Take 1 to 2 droppersful in tea or water 1 to 3 times daily as needed. Continuous high-level consumption of this product for more than 2 weeks of each month is not recommended.	0.8 - 4.8 mL	Not recommended for pregnant or nursing women.
Cytoplan Organic Echinacea	Oral solution	<i>Echinacea angustifolia</i>	1:3 extract	Take 20 drops mixed into water or liquid of choice 2-3 times daily. 20 drops = 2mL.	40-60 drops daily. Equivalent to 4-6 mL extract daily.	Not suitable for children under 12 years of age. Not suitable for use whilst pregnant or breastfeeding.

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Table 10: Combined acute exposure scenarios for the consumption 4-5 products of *Echinacea* (as dried root/herb) during pregnancy.

Estimated exposure to *Echinacea* (mg/day)

Tea	Honey	Lozenges	Tablets/capsules	Oral liquids	Total consumed per day
860 - 6,000	19 - 100	40	400 - 3,600	600 - 3,000	1,900 - 13,000
N/A	19 - 100	40	400 - 3,600	600 - 3,000	1,100 - 6,700
860 - 6,000	N/A	40	400 - 3,600	600 - 3,000	1,900 - 13,000
860 - 6,000	19 - 100	N/A	400 - 3,600	600 - 3,000	1,900 - 13,000
860 - 6,000	19 - 100	40	N/A	600 - 3,000	1,500 - 9,100
860 - 6,000	19 - 100	40	400 - 3,600	N/A	1,300 - 9,700

*Rounded to 2 significant figures.

Table 11: Combined acute exposure scenarios for the consumption of 3 products of *Echinacea* (as dried root/herb) during pregnancy.

Estimated exposure to *Echinacea* (mg/day)

Tea	Honey	Lozenges	Tablets/capsules	Oral liquids	Total consumed per day
860 - 6,000	19 - 100	40	N/A	N/A	920 - 6,100
860 - 6,000	19 - 100	N/A	400 - 3,600	N/A	1,300 - 9,700
860 - 6,000	19 - 100	N/A	N/A	600 - 3,000	1,500 - 9,100
860 - 6,000	N/A	N/A	400 - 3,600	600 - 3,000	1,900 - 13,000
860 - 6,000	N/A	40	400 - 3,600	N/A	1,300 - 9,600
860 - 6,000	N/A	40	N/A	600 - 3,000	1,500 - 9,000

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N/A	N/A	40	400 - 3,600	600 - 3,000	1,000 - 6,700
N/A	19 - 100	N/A	400 - 3,600	600 - 3,000	1,000 - 6,700
N/A	19 - 100	40	400 - 3,600	N/A	460 - 3,700
N/A	19 - 100	40	N/A	600 - 3,000	660 - 3,100

*Rounded to 2 significant figures.

Table 12: Combined acute exposure scenarios for the consumption of 2 products of Echinacea (as dried root/herb) during pregnancy.

Estimated exposure to Echinacea (mg/day)

Tea	Honey	Lozenges	Tablets/capsules	Oral liquids	Total consumed per day
860 - 6,000	19 - 100	N/A	N/A	N/A	900 - 6,100
860 - 6,000	N/A	40	N/A	N/A	900 - 6,000
860 - 6,000	N/A	N/A	400 - 3,600	N/A	1,300 - 9,600
860 - 6,000	N/A	N/A	N/A	600 - 3,000	1,500 - 9,600
N/A	19 - 100	40	N/A	N/A	60 - 140
N/A	19 - 100	N/A	400 - 3,600	N/A	420 - 3,700
N/A	19 - 100	N/A	N/A	600 - 3,000	620 - 3,100
N/A	N/A	40	400 - 3,600	N/A	440 - 3,600
N/A	N/A	40	N/A	600 - 3,000	640 - 3,000
N/A	N/A	N/A	400 - 3,600	600 - 3,000	1,000 - 6,600

*Rounded to 2 significant figures.

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Table 13: *Echinacea* products (oral dosage forms) with THR in the UK.

Product name	Dosage form	<i>Echinacea</i> species and plant part	Composition	Directions for use	Daily dose <i>Echinacea</i> (mg)
Echinaflu Soft Capsules	Capsules	<i>Echinacea purpurea</i> (L.) Moench herb	176 mg of dried pressed juice from fresh flowering herb equivalent to 3.5-4.9 g of fresh herb (DER 20-28:1).	1-2 capsules daily for no longer than 10 days.	176 - 352 mg dried pressed juice equivalent to 3.5 - 9.8 g fresh herb.
Echinacea Cold and Flu Capsules	Capsules	<i>Echinacea purpurea</i> (L.) Moench) root	140 mg dry extract from root equivalent to 838 - 1117 mg root (DER 6-8:1).	1 capsule twice a day.	280 mg dry root extract equivalent to 1,676- 2,234 mg root.
Ekinalife	Capsules	<i>Echinacea pallida</i> (Nutt.) Nutt. root and <i>Echinacea purpurea</i> (L.) Moench root	200mg of <i>Echinacea pallida</i> . Nutt. and 200mg of <i>Echinacea purpurea</i> (L.) Moench powdered root.	1 capsule twice a day for no longer than 10 days.	400 mg <i>E. pallida</i> powdered root and 400 mg <i>E. purpurea</i> powdered root. Total of 1,600 mg powdered root.
Solgar Echinacea Cold and Flu Capsules	Capsules	<i>Echinacea purpurea</i> (L.) Moench root	140 mg dry extract from root equivalent to 838 - 1117 mg root (DER 6-8:1).	1 capsule twice a day for no longer than 10 days.	280 mg dry root extract equivalent to 1,676- 2,234 mg root.
Phytocold	Capsules	<i>Echinacea purpurea</i> (L.) Moench root	250 mg powdered root.	1-2 capsules three times a day fo no longer than 10 days.	750 - 1,500 mg powdered root.
Echinaflu Effervescent Tablets	Effervescent Tablets	<i>Echinacea purpurea</i> (L.) Moench herb	176 mg of dried pressed juice from fresh flowering herb equivalent to 3.5-4.9 g of fresh herb (DER 20-28:1).	1-2 tablets daily for no longer than 10 days.	176 - 352 mg dried pressed juice equivalent to 3.5 - 9.8 g fresh herb.
Echineeze	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	70 mg dry extract from root equivalent to 460 – 530 mg root (DER 6.5-7.5:1).	1 tablet 3 times a day for no longer than 10 days.	210 mg dry root extract equivalent to 1,380 - 1,590 mg root.

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Echinaforce Forte Cold & Flu Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench herb and root	1,140 mg dry extract from fresh herb (DER 1:12) and 60 mg (DER 1:11) dry extract from fresh root.	1 tablet two to three times a day for no longer than 10 days.	2,280 - 3,420 mg dry herb extract and 120-180 mg dry root extract.
Herbal Cold And Flu Relief Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	71.5 mg dry extract from root equivalent to 429 - 500 mg root (DER 6-7:1).	1-2 tablets twice daily for no longer than 10 days.	143-286 mg dry root extract equivalent to 858 - 2,000 mg root.
High Strength Herbal Cold And Flu Relief Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	143 mg dry extract from root equivalent to 858 - 1000 mg root (DER 6-7:1).	1 tablet three times a day for no longer than 10 days.	429 mg dry root extract equivalent to 2,574 - 3,000 mg root.
Echinacea Skin Care Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	71.5 mg dry extract from root equivalent to 429 - 500 mg root (DER 6-7:1).	1-2 tablets three times a day for no longer than 10 days.	143-286 mg dry root extract equivalent to 858 - 2,000 mg root.
Herbal Classics Echinacea Cold Relief Film-Coated Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	40 mg dry extract from root equivalent to 260 mg root (DER 6.5:1).	2-3 tablets three times a day.	240-360 mg dry root extract equivalent to 1,560 -2,340 mg root.
HRI Cold And Flu Echinacea Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	56 mg dry extract from root equivalent to 338 - 450 mg root (DER 6-8:1).	1-2 tablets twice daily.	112-224 mg dry root extract equivalent to 676-1,800 mg root.
Echinapret Coated Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench herb	175 mg of dried pressed juice from fresh flowering herb equivalent to 6.7 - 9.8 g fresh herb (DER 38 - 56:1).	1 tablet three times a day for no longer than 10 days.	525 mg dried pressed juice equivalent to 18.4 - 29.4 mg fresh herb.
Thompson and Capper Echinacea	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	105 mg dry extract from root equivalent to 630 - 840 mg root (DER 6-8:1).	1 tablet twice a day for no longer than 10 days.	210 mg dry root extract equivalent to 1,260 -1,680 mg root.

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Cold-n-Flu-Eze					
Fuerte Tablets	Tablets	Wild indigo root (<i>Baptisia tinctoria</i> (L.) R.Br.), <i>Echinacea purpurea</i> root (<i>Echinacea purpurea</i> (L.) Moench), <i>Echinacea pallida</i> root (<i>Echinacea pallida</i> (Nutt.) Nutt.) , White cedar tips and leaves (<i>Thuja occidentalis</i> L.)	3.2 mg dry root extract (DER 4-9:1) from Wild indigo root, <i>E. purpurea</i> root, <i>E. pallida</i> root and Wild cedar tips and leaves (4.92:1.85:1.85:1)	5 tablets three times a day for no longer than 10 days.	9.2 mg <i>E. pallida</i> and 9.2 mg <i>E. purpurea</i> dry root extract. Total 18.4 mg dry root extract equivalent to 73.6-165.6 mg root.
Healthsense Echinashield Cold and Flu Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	70 mg dry extract from root equivalent to 420 - 560 mg root (DER 6-8:1).	1 tablet three times a day for no longer than 10 days.	210 mg dry root extract equivalent to 1,260 -1,680 mg root.
Lamberts Echinacea Cold & Flu relief tablets Nature's Best Echinacea Cold & Flu Relief tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	105 mg dry extract from root equivalent to 630 - 840 mg root (DER 6-8:1).	1 tablet twice a day for no longer than 10 days.	210 mg dry root extract equivalent to 1,260 -1,680 mg root.
Vitabiotics Echinacea Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	200 mg dry extract from root equivalent to 1200 - 1600 mg root (DER 6-8:1).	1 tablet twice a day for no longer than 10 days.	400 mg dry root extract equivalent to 2,400 -3,200 mg root.

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Potter's Skin Clear Tablets	Tablets	<i>Echinacea angustifolia</i> (D.C) root	110 mg dry extract from root equivalent to 500 mg root (DER 4.5:1).	2 tablets three times a day for no longer than 10 days.	660 mg dry root extract equivalent to 2,970 mg root.
EKINACLEA R	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	50 mg dry extract from root equivalent to 300 - 400 mg root (DER 6-8:1).	1-2 tablets three times a day for no longer than 10 days.	150-300 mg dry root extract equivalent to 900-2,400 mg root.
Lifeplan Echinacea Cold and Flu Relief Tablets	Tablets	<i>Echinacea purpurea</i> (L.) Moench root	140 mg dry extract from root equivalent to 840 - 1120 mg root (DER 6-8:1).	1 tablet twice a day for no longer than 10 days.	150-300 mg dry root extract equivalent to 900-2,400 mg root.
Echinaforce Chewable Cold & Flu Tablets	Chewable tablets	<i>Echinacea purpurea</i> (L.) Moench herb and root	380 mg dry extract from fresh herb (DER 1:12) and 20 mg dry extract (DER 1:11) from fresh root.	2 tablets two to three times a day for no longer than 10 days.	1,520 - 2,280 mg dry herb extract and 80-120 mg dry root extract.
Herbal Cold And Flu Sachets	Sachets	<i>Echinacea purpurea</i> (L.) Moench root	71.5 mg dry extract from root equivalent to 429 - 500 mg root (DER 6-7:1).	1 sachet three times a day for no longer than 10 days.	214.5 mg dry root extract equivalent to 1,287-1,500 mg root.
Cystorelief Cystitis Uva-ursi & Echinacea oral drops ^a	Tincture	<i>Echinacea purpurea</i> (L.) Moench herb, Uva-ursi herb (<i>Arctostaphylos uva-ursi</i> (L.) Spreng, Herb)	240 mg of tincture from fresh herb (DER 1:12) per 1 mL.	15 drops in a little water 2-5 times daily. 1mL is equivalent to 30 drops.	240-600 mg of tincture from fresh herb.
Potter's Elixir of Echinacea Plus/Napiers Elixir of Echinacea Complex ^b	Oral solution	<i>Echinacea angustifolia</i> (D.C) root, Wild Indigo root, Fumitory herb	0.64 mL liquid extract from root equivalent to 640 mg root per 5 mL (DER 1:1).	5 mL three times a day for no longer than 10 days.	1.92 mL liquid root extract equivalent to 1.92 g root.

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Echinacin Juice MADAUS	Oral solution	<i>Echinacea purpurea</i> (L.) Moench) herb	117 mg of dried pressed juice from fresh flowering herb equivalent to 3.7 - 6.3 g of fresh herb per 5 mL (DER 31.5-53.6:1).	5 mL three times a day for no longer than 10 days.	351 mg dried pressed juice equivalent to 11.1 - 18.9 g fresh herb.
Echinacin Liquidum MADAUS ^c	Oral solution	<i>Echinacea purpurea</i> (L.) Moench) herb	1.99 g of pressed juice from fresh flowering herb equivalent to 3.4 - 5 g of fresh herb per 2.5 mL (DER 1.7-2.5:1).	2.5 mL three times a day for no longer than 10 days.	5,970 mg pressed juice equivalent to 10.2-15 g fresh herb.
Echinaforce hot drink cold & flu echinacea concentrate for oral solution	Tincture	<i>Echinacea purpurea</i> (L.) Moench herb and root	1,140 mg extract (as tincture) from fresh herb (DER 1:12-13) and 60 mg extract (as tincture) from fresh root (DER 1:11-12) per 5 mL.	Days 1-3: Take 5 ml diluted in hot water five times daily. Days 4-10: Take 5 ml diluted in hot water three times daily.	3,420 - 5,700 mg herb extract (tincture) and 180-300 mg root extract (tincture).
Echinaforce Sore Throat Spray ^d	Oromucosal spray	<i>Echinacea purpurea</i> (L.) Moench herb and root, Sage leaves, (<i>Salvia officinalis</i> L. <i>folium</i>)	863.3 mg tincture from fresh herb (DER 1:12) and 45.5 mg tincture from fresh root (DER 1:11) per 1 mL.	1 spray (0.22 mL) six to ten times a day for no more than 7 days.	1,147 - 1,910 mg herb tincture and 60 - 100 mg root tincture.
Duchy Herbals Echina-Relief Tincture ^e	Tincture	<i>Echinacea purpurea</i> (L.) Moench root	1mL of tincture from dried root (1:3) (equivalent to 33 mg dried root) per 1 mL tincture.	2.5 ml of tincture, in water, two or three times daily for no longer than 10 days.	5-7.5 mL tincture equivalent to 165 - 248 mg dried root.

^a 1 mL contains 426 mg ethanol equivalent to 10.8 mL beer or 4.5 mL wine (43% v/v ethanol content).

^b 5 mL contains 760 mg ethanol equivalent to 19 mL beer or 7.9 mL wine (19 % v/v ethanol content).

^c 1 mL contains 179 mg ethanol equivalent to 4 mL beer or 1.6 mL wine (18% v/v ethanol content).

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^d 1 mL contains 370 mg ethanol equivalent to 8.4 mL beer or 3.4 mL wine (38-42% v/v ethanol content).

^e 2.5 mL contains 900 mg ethanol equivalent to 23 mL beer or 10 mL wine (38-45% v/v ethanol content).

Table 14: Summary of doses and preparations of THR products in the UK and EMA monographs.

<i>Echinacea</i> species	Daily dose THR products UK	EMA monographs daily doses
<i>Echinacea purpurea</i>	<p>Pressed juice from herb (DER 1.7-2.5:1): 5,970 mg (equivalent to 10.2-15 g fresh herb).</p> <p>Dried pressed juice from herb (DER 20-28:1): 176-352 mg (equivalent to 3.5 - 9.8 g fresh herb).</p> <p>Dry root extract (DER 6-7:1): 143 - 429 mg (equivalent to 858 - 3,000 mg root).</p> <p>Powdered root: 250 -1500 mg.</p>	<p>Pressed juice from herb (DER 1.5-2.5:1): 6 - 9 g (equivalent to 9 - 22.5 g fresh herb).</p> <p>Dried pressed juice: Corresponding to the expressed juice above (EMA monograph, 2014).</p> <p>Dry root extract (DER 5.5-7.5:1): 360 mg (equivalent to 1,980 - 2,700 mg root). (EMA monograph, 2017).</p>
<i>Echinacea angustifolia</i>	<p>Dry root extract (DER 4.5:1): 660 mg equivalent to 2,970 mg root.</p> <p>Liquid root extract (DER 1:1): 1.92 mL (equivalent to 1,920 mg root).</p>	<p>Powdered root: 500-1,500 mg.</p> <p>Liquid root extract (DER 1:1): 0.75 - 3 mL (equivalent to 750 -3,000 mg root).</p> <p>Tincture (DER 5:1): 3-6 mL (equivalent to 1,500 - 3,000 mg root). (EMA monograph 2018).</p>

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<i>Echinacea pallida</i>	Dry root extract (DER 4-9:1): 9.2 mg <i>E. pallida</i> and 9.2 mg <i>E. purpurea</i> (equivalent to 36.8-82.8 mg root). Powdered root: 400 mg <i>E. pallida</i> and 400 mg <i>E. purpurea</i> .	Dry root extract (DER 4-8:1): 90-96 mg (equivalent to 360 - 786 mg root) (EMA monograph 2012).
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