TOX/2025/45

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

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

Introduction

1. In 2020 the COT considered a scoping paper (TOX/2020/51) that reviewed commonly used herbal supplements during pregnancy. This was part of COT's ongoing programme to assess the potential risks from the maternal diet, intended to support the Scientific Advisory Committee on Nutrition's (SACN) review of nutrition and maternal health, focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery.

2. The scoping paper (TOX/2020/51) was confined to herbal dietary supplements which would be regulated as foods and which would not be considered to be traditional herbal medicines within the remit of the Medicines and Healthcare products Regulatory Agency (MHRA). Among those investigated was *Echinacea*, which is commonly used for immune support, prevention of colds and treatment of cold and flu-like symptoms.

3. In December 2024, a discussion paper on the effects of *Echinacea* on maternal health was presented to the Committee (TOX/2024/43). This paper reviewed the available data from *in vitro*, *in vivo* and human studies covering the mechanisms of action of *Echinacea*, drug-herb interactions, presence of contaminants, toxicity including genotoxicity, reproductive and developmental toxicity and the adverse effects of *Echinacea* reported in human studies. The limited information available on human exposures to *Echinacea* during pregnancy was also discussed.

4. The Committee considered the risk to maternal health from *Echinacea* exposure during pregnancy likely to be low but highlighted that there was insufficient information to enable a robust risk assessment. Members agreed that the point of departure 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. It was also acknowledged that individuals with atopic disease or autoimmune disorders will be at higher risk from exposure to *Echinacea* products than the general population and this should be taken into account for the risk assessment.

5. Members noted that many of the food supplements suggest a short-term use of *Echinacea* and that this should be more clearly emphasised within the exposure section. The transient exposure makes it difficult to accurately estimate the percentage of women using *Echinacea* at different stages of pregnancy and assess the implications of extrapolating findings from diverse study designs.

6. The COT Members commented that the paper would benefit from a clearer segmentation of the reproductive and developmental data to highlight any data gaps in the reproductive and developmental window covered when considering the safety of *Echinacea* in the maternal diet. It was suggested that this could be done in the form of a table or schematic summary of the reproductive and developmental end points covered by the animal and human studies available.

7. Members also requested a clarification on the scope of the maternal health project, particularly regarding the stages of the reproductive and developmental cycle assessed. This has been incorporated in a separate Annex entitled Scope of the Nutrition and maternal health project (please see Annex A to TOX/2025/44).

8. The COT Members agreed there was lack of high-quality available data on the reproductive end points from both animal and human studies. A potential data gap identified by Members was the absence of studies looking at the 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.

9. Members discussed the *in vivo* mice study by Chow *et al*. (2006) and the epidemiological study by Gallo *et al.* (2000) in more detail. They considered that the conclusion reached by Chow *et al*. (2006) that *Echinacea* could lead to miscarriages in early pregnancy was not convincing as the authors used a mouse strain (DBA) with small litter size and they did not provide any range/standard deviation with their results on foetal loss. Members commented that the sample size (n=206) in the study by Gallo *et al.* (2000) would not give sufficient statistical power to detect the birth defects and malformations studied.

10. Members also commented 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. It was suggested that that this should be added as a caveat in the risk characterisation section.

11. COT Members also emphasised the need for clearer structuring of data, including tables and summaries for complex and conflicting findings. This was particularly relevant for the section on the immunomodulatory effects of *Echinacea*, which contained information on variety of effects exerted by *Echinacea* on different immune system cell types and subsequent cytokine production. The Members also suggested that the anti-inflammatory and immunomodulatory effects of *Echinacea* should be considered in the same section rather than as separate items.

12. A section on the pharmacokinetics of *Echinacea* constituents has been added to this draft statement.

13. A draft Statement has been prepared, incorporating Members' comment, which is included at Annex A. It was suggested that the statement should

make a clear distinction between the conclusions reached by the individual studies and the COT conclusions.

Questions for the Committee

The Committee are asked to consider the following questions:

a) Does the Committee have any comments on the structure or content of the draft Statement?
b) Does the Committee agree with the risk characterisation and conclusions sections?
c) Does the Committee have any other comments on the draft Statement?

Secretariat

December 2025

Annex A to TOX/2025/45

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

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Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) last considered the maternal diet and nutrition in relation to offspring health in its reports on 'The influence of maternal, foetal and child nutrition on the development of chronic disease in later life' (SACN, 2011) and on 'Feeding in the first year of life' (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health, focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery. Further information on the scope of the maternal health projects can be found in the Scope of the Nutrition and maternal health project Annex (Annex A to TOX/2025/44).

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

3. As part of this work, the Committee decided it would be useful to consider the use of dietary supplements during pregnancy. A scoping paper (TOX/2020/51) was presented, reviewing the dietary supplements commonly used during pregnancy.

These supplements are not officially recommended by relevant health and regulatory authorities but are promoted by anecdotal evidence and unofficial sources as having various purported benefits.

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

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

Background

Uses

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

7. *Echinacea* herbal products are often sold as dietary supplements to enhance the immune function and to reduce the symptoms and duration of common cold and upper respiratory tract infections. These are popular products in North America and

Europe, generating more than 300 million USD annually in the U.S. alone (Ahmadi *et al*., 2024).

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

Constituents and preparations

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

10. The composition of bioactive metabolites varies across the three medicinally used species and their respective plant parts. It is generally considered that there is no single constituent or group of constituents responsible for the activity of *Echinacea*. The combined effects of several groups of bioactive constituents, 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.

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).

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

16. The EMA assessment report on *E. angustifolia* specifies that, according to the European Pharmacopoeia, *Echinaceae angustifoliae* radix consists of the whole or cut, dried underground parts of *E. angustifolia* DC and must contain not less than

0.5% echinacoside. The EMA report details that major constituents of *E. angustifolia* root include caffeic acid derivatives (1.0–1.4%), cynarin (0.12–0.14%), chlorogenic acid and cichoric acid. Alkylamides are present at about 0.5%, mainly as isobutylamides and 2-methylbutylamides of straight-chain fatty-acids with olefinic and/or acetylenic bonds e.g. isomeric dodeca-2E,4E,8Z,10E/Z-tetraenoic isobutylamide. The root also contains polysaccharides and glycoproteins, including two polysaccharides (128 kDa and 4.5 kDa) and three glycoproteins (17–30 kDa), with the dominant sugars being arabinose (64–84%), galactose (2–5%), and glucosamine (6%). Volatile oils occur in small amounts (~0.1%) and include dodeca-2,4-diene-1-yl isovalerate and pentadeca-1,8Z-diene. Other constituents include phytomelanin and trace levels of saturated pyrrolizidine-type alkaloids (tussilagine and isotussilagine, approximately 0.006%) (EMA, 2012). The herbal preparation for traditional use consists of comminuted or powdered herbal substance, tincture (ratio of herbal substance to extraction solvent 1:5) or liquid extract (DER 1:1). Both tincture and liquid extract are obtained with 45% v/v ethanol extraction solvent (EMA monograph, 2012).

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

18. Studies on reproductive toxicity, genotoxicity and carcinogenicity had not been performed for preparations of *E. pallida* (EMA, 2018) or *E. angustifolia* (EMA, 2012) at the time the EMA reports were written. In the absence of these data, the use of these species in pregnancy and lactation was not recommended by EMA.

Due to the lack of genotoxicity data, the EMA did not recommend the addition of *E. pallida* (EMA, 2018) and *E. angustifolia* (EMA, 2012) to the Community list of herbal substances, herbal preparations and combinations thereof for traditional medicinal products. There were also insufficient clinical data to support the criteria for well-established medicinal use of *E. angustifolia* and *E. pallida* roots, in accordance with Directive 2001/83/EC. The traditional use of *E. angustifolia* and *E. pallida* root extracts for the relief of common cold symptoms was deemed as acceptably safe by EMA due to longstanding history of use without reports of serious adverse effects.

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

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

Health-based guidance values (HBGVs)

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

Pharmacokinetic studies

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 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. On day 15, plasma levels of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (DTAI) were measured. The peak plasma concentration was reached 30 minutes post-dose with C_{max} values of 0.04–0.18 ng/mL. 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 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. Nine healthy volunteers 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) immediately after a high fat breakfast (Matthias *et al*. 2005). 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 concluded that alkylamides from *Echinacea* preparations were orally bioavailable and their pharmacokinetics supported the three times daily regimen already recommended for *Echinacea.*

Drug-herb interaction potential: 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) and P-glycoprotein (Husain *et al*., 2023; Hansen and Nilsen, 2009). Some of the *in vitro* studies reported a positive association between the total alkylamide content of the *Echinacea* preparation and its ability to inhibit CYP3A4 (Modarai *et al*. 2010) and CYP1A2 (Raner *et al*. 2007).

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

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. No serious adverse events occurred during the course of the study; one subject experienced a mild rash while taking *Echinacea.* 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).

Toxicity Studies

In vitro and in vivo studies

Acute toxicity

E. purpurea

30. No adverse effects were observed when expressed juice from *E. purpurea* was administered either orally or intravenously to 8 week old Wistar rats and NMRI mice following Good Laboratory Practice (GLP) and the OECD recommendations for technical methods at the time of the study (Mengs *et al*., 1991). Eight animals of each sex were given a single oral dose *via* gastric tube 15,000 mg/kg bw in rats and 30,000 mg/kg bw in mice. The intravenous dose was administered to eight animals of each sex *via* the tail vein at 5,000 mg/kg bw in rats and 10,000 mg/kg bw in mice. The animals were observed for 14 days and inspected several times daily and at the end of the experiment a necropsy with macroscopic inspection was performed. There were no deaths or any signs of abnormalities or toxicity due to the *Echinacea*. The authors concluded that a lethal dose cannot be found and LD_{50} was not calculated.

E. angustifolia

31. An acute toxicity study was performed with *E. angustifolia* following the OECD-423 criteria (Espinosa-Paredes *et al*., 2021). Briefly, three CD-1 male mice received a single dose of 2,000 mg/kg bw of the ethyl acetate extract and were monitored for 14 days for clinical signs and mortality. No adverse effects such as piloerection, mucosal irritation, altered motor activity, or death were observed. Necropsy revealed no macroscopic lesions in major organs, including lungs, kidneys, heart, stomach, intestines, spleen, and liver. Based on these findings, the authors classified the LD_{50} of the ethyl acetate extract as Category 5 under the Globally

Harmonized System (GHS) (>2,000–5,000 mg/kg), indicating very low acute toxicity and potential risk only for vulnerable populations.

Subacute toxicity

E. purpurea

32. Expressed juice from *E. purpurea* was administered *via* oral gavage to groups of 18 Wistar rats per sex at doses of 0, 800, 2,400, or 8,000 mg/kg body weight daily for four weeks (Mengs *et al*., 1991). A statistically significant reduction in plasma alkaline phosphatase was observed in males at 2,400 and 8,000 mg/kg, while females exhibited a significant increase in prothrombin time at the same dose levels compared to controls. The authors concluded that since the alkaline phosphatase and prothrombin time were still in the normal physiological variation range for the rat strain used and there was no dose dependent response, no toxicological point of departure could be derived from the data. The study noted 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.

E. angustifolia

33. Espinosa-Paredes *et al*. (2021) conducted a 28-day repeated-dose toxicity study with ethyl acetate extract of *E. angustifolia*. The extract was administered to five CD-1 mice per dose per sex at 20 mg/kg bw or 200 mg/kg bw. 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 *Echinacea* extract administration.

Sub-chronic toxicity

34. 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 compliance with GLP regulations and the Korean Food and Drug Administration's Test Guidelines for Toxicity Studies of Drugs. The *E. purpurea* extract, standardised to contain at least 2% chicoric acid, was administered daily at

doses of 0, 500, 1,000, and 2,000 mg/kg body weight to groups of 10 rats per sex. No mortality or abnormal clinical signs were observed in either sex at any of the tested doses. 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 they were not significantly different when compared to the controls.

Cytotoxicity

35. 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.

Genotoxicity

E. purpurea

36. No genotoxic effects were observed in an *in vitro* bacterial reverse mutation assay, a mouse lymphoma assay, human lymphocyte assay and a micronucleus test performed by Mengs *et al*. (1991) using lyophilised *E. purpurea* expressed juice from the commercial product Echinacin Liquidum. The GLP OECD guidelines and the OECD recommendations for technical methods at the time of the study were followed. Details of the Mengs *et al*. (1991) tests and the authors conclusions are provided below.

37. The bacterial reverse mutation test evaluated lyophilised *E. purpurea* expressed juice at 8–5,000 µg/plate in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, with and without S9 metabolic activation. No dose-related or statistically significant increase in revertant colonies was observed, indicating no mutagenic activity.

38. The mouse lymphoma assay involved testing lyophilised *E. purpurea* expressed juice concentrations of 50–5,000 µg/mL in L5178Y mouse lymphoma cells, with and without S9 metabolic activation. No significant increase in mutation frequency was detected at any concentration, and the test material was virtually non-toxic up to 5,000 µg/mL.

39. For the *in vitro* chromosomal aberration test, the lyophilised Echinacin Liquidum was tested at 2,400–5,000 µg/mL in human lymphocyte cultures, with and without S9 metabolic activation. There was no evidence of mitotic inhibition following the *Echinacea* treatment of up to 5,000 µg/mL A small, but statistically significant increase in the proportion of cells with structural aberrations was observed at 5,000 µg/mL at the 20 h sampling point in the absence of S9, but it was considered biologically insignificant by the authors as it well within the range of biological control.

40. The *in vivo* micronucleus test involved the administration of Echinacin Liquidum orally at 25,000 mg/kg to 5 male and 5 female mice. Bone marrow analysis at 24, 48, and 72 h post-dose showed no significant increase in micronucleated polychromatic erythrocytes compared to controls.

41. An *in vitro* cell transformation assay was performed using lyophilised *E. purpurea* extract using Syrian hamster embryo cells (SHE) (Mengs *et al*., 1991). Six concentrations (5–55 µg/mL) were tested in two independent experiments (20 replicates per concentration), with benzo(a)pyrene as a positive control. After 7 days of incubation, colonies were evaluated for morphological transformation. The study reported no significant difference in the frequencies of morphologically transformed colonies between the treatment groups and the negative control, and the authors concluded that there was no evidence of malignant transformation induced by *Echinacea* extract.

42. The mutagenicity and the antimutagenic effects of *E. purpurea* were tested in *S. typhimurium* TA 98 and TA 100 strains with and without S9 metabolic activation at a maximum concentration of 5 mg/plate (Tsai *et al*., 2012b). The *E. purpurea* extracts showed no toxicity against *S. typhimurium* strains TA98 and TA100 concentrations of ≤5.0 mg/plate, with or without S9 metabolic activation (Tsai *et al*., 2012b). None of the tested concentrations of *E. purpurea* showed any significant differences in the revertant number with or without S9 mix. The *Echinacea* extract however showed a dose-dependent inhibitory effect on the mutagenicity of 2-aminoanthracene in both *S. typhimurium* strains.

43. Jeong *et al*. (2024) assessed the genotoxic potential of *E. purpurea* extract using three assays: an *in vitro* bacterial reverse mutation test (OECD 471), an *in vitro* chromosomal aberration test (OECD 473), and an *in vivo* micronucleus test (OECD 474). For the bacterial reverse mutation assay, the extract was tested up to 5,000 µg/plate in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* WP2uvrA, with and without S9 activation. No growth inhibition or increase in revertant colonies was observed at any dose and results were considered negative for mutagenicity. For the *in vitro* chromosomal aberration test, Chinese Hamster Lung (CHL/IU) cells were treated with up to 313 µg/mL extract, with or without metabolic activation. No statistically significant increase in structural or numerical chromosomal aberrations was observed compared to controls. In the *in vivo* micronucleus test, seven-week-old male Sprague Dawley rats received *E. purpurea* extract at 1,250–5,000 mg/kg bw (two doses; 5 animals per dose). Bone marrow analysis showed no statistically significant increase in micronucleated polychromatic erythrocytes compared to negative controls. Based on these findings, the authors concluded that no evidence of genotoxicity was observed across all three assays.

E. angustifolia

44. The mutagenicity of *E. angustifolia* was tested using an *in vitro* bacterial reverse mutation test in *S. typhimurium* TA98, TA100 and TA102 in the presence and absence of S9 metabolic activation mix (Espinosa-Paredes *et al*., 2021). 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 test and no genotoxic activity was therefore observed.

45. Espinosa-Paredes *et al*. (2021) conducted an *in vivo* micronucleus test in male CD-1 mice to assess genotoxicity of an ethyl acetate extract of *E. angustifolia* administered intragastrically at 1,000 mg/kg bw to three animals. 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 *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.

Reproductive and developmental effects of *Echinacea*

46. There are limited data from animal and human studies on the reproductive and developmental effects of *Echinacea* and its subsequent safety during pregnancy and lactation. The stages of the reproductive and developmental cycle covered by the available animal and human studies on the effects of *Echinacea* during the reproductive and developmental period are outlined in Table 1. Further information on the reproductive and developmental cycle stages and the scope of the maternal diet papers can be found in Scope of the Nutrition and maternal health project Annex (TOX/2025/44).

Table 1: Reproductive and developmental cycle stages covered by available *Echinacea* animal and human studies.

Study reference	**Study type**	***Echinacea* preparation and dose**	**Stage A (pre-mating to conception)**	**Stage B (conception to implantation)**	**Stage C (implantation to closure of hard palate)**	**Stage D (closure of hard palate to end of pregnancy)**	**Stage E (birth to weaning)**	**Stage F (weaning to sexual maturity)**
Chow *et al*. 2006	Animal study (DBA/2 mice)	*E. purpurea* extract 0.45 mg/kg bw/day (dose per body weight)	Not covered	Covered	Covered	Covered	Not covered	Not covered
Barcz *et al*. 2007	Animal study (Balb/c mice)	*E. purpurea* extract 0.6 mg/day	Not covered	Covered	Covered	Covered	Not covered	Not covered
Khaksary Mahabady *et al*., 2006	Animal study (NMRI mice)	*E. purpurea* extract 360 mg/kg	Not covered	Covered	Covered	Covered	Not covered	Not covered
Maass *et al*., 2005)	Animal study (pigs)	*E. purpurea* dried cobs 0.5-3.6%	Not covered	Not covered	Not covered	Covered	Covered	Not covered
Dabbou *et al*., 2016	Animal study (rabbits)	*E. pallida* 3 g/kg	Not covered	Covered	Covered	Covered	Covered	Not covered
Kovitvadhi *et al*., 2016	Animal study (rabbits)	*E. pallida* 3 g/kg	Not covered	Not covered	Not covered	Not covered	Not covered	Covered

Gallo *et al*., 2000	Human prospective controlled study	*E. purpurea* and *E. angustifolia* 250- 1000 mg/day	Unknown	Covered	Covered	Covered	Not covered	Not covered
Heitmann *et al*., 2016	Human prospective cohort study	Not known	Unknown	Covered	Covered	Covered	Not covered	Not covered
Cuzzolin *et al*., 2010	Human cross-sectional study	Not known	Unknown	Unknown	Unknown	Unknown	Not covered	Not covered
Nordeng *et al*., 2011	Human cross-sectional study	Not known	Unknown	Unknown	Unknown	Unknown	Not covered	Not covered
Matthias *et al*., 2008	Human case report	Four tablets each containing *E. purpurea* 675 mg and *E. angustifolia* 600 mg	Not covered	Not covered	Not covered	Not covered	Covered	Not covered

*See Annex Scope of the Nutrition and maternal health (TOX/2025/44) for further information on reproductive and developmental cycle.

Animal studies

47. There are no guidelines 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

48. Chow *et al*. (2006) investigated the potential association between *E. purpurea* consumption and spontaneous abortion in pregnant DBA/2 mice. Six mice were fed *Echinacea*-supplemented chow from conception and sacrificed at either gestational days 10–11 (early pregnancy) or 12–14 (mid pregnancy). Commercially prepared *E. purpurea* extract was homogenized into finely ground standard chow that individual mice consumed *Echinacea* at 0.45 mg/kg bw/day. *Echinacea*-fed mice showed reduced spleen lymphocytes and nucleated erythroid cells, aligning with levels in non-pregnant mice. 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 treatment group). The authors concluded that *Echinacea* may increase miscarriage risk in early pregnancy and advised against its use during this period.

49. Barcz *et al*. (2007) investigated the effects of *Echinacea* on the angiogenic activity and tissue vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in foetuses from pregnant Balb/c mice exposed to *E. purpurea* extracts. Eight mice received 0.6 mg of *Echinacea* extract daily from fertilisation to gestation day 18 (three Esberitox, two Immunal, three Echinapur). On day 18, foetuses were collected, pooled, and analysed. 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 ($p < 0.0001$). Angiogenic activity increased significantly in the Esberitox group, decreased in the Immunal group, and remained unchanged with Echinapur. The study concluded that *E. purpurea* preparations may influence foetal angiogenesis and should not be recommended in pregnancy without further studies being carried out.

50. 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.

51. 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. No adverse effects were observed in sows or piglets. While sows in the control group gained more weight during gestation, no significant differences were found in lactation weight loss, piglet birth weight, or growth performance. The study concluded that *Echinacea* supplementation had no significant impact on sow or piglet health.

E. pallida

52. 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/kg *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 concluded that supplementation with *E. pallida* did not show any significant effects on the reproductive, haematological, or immune parameters of does.

53. The second study (Kovitvadhi *et al*., 2016) assessed the offspring of these does. Eighty weaned kits were allocated into four groups based on maternal diet and post-weaning diet: (1) offspring from control does fed the control diet, (2) offspring from control does fed the 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/kg). Parameters measured included growth, microbiome composition, blood biochemistry, phagocytic activity, and humoral immune response. While phagocytosis increased in supplemented groups, no significant differences were found in other outcomes. The study concluded that there were no significant differences in growth performances, blood parameters, bacterial community, or humoral immune response in the offspring.

Human studies

54. A systematic review conducted on the available literature up to 2006 (Perri *et al*., 2006) concluded that good scientific evidence from a prospective follow up study (Gallo *et al*., 2000) showed that oral consumption of *Echinacea* during the first trimester did not increase the risk of major malformations. Perri *et al* (2006) noted that The German Commission E compendium produced by an expert panel on a botanical medicine (Blumenthal *et al*., 1998) had concluded that *Echinacea* was not teratogenic and oral consumption of *Echinacea* in recommended doses was safe during pregnancy and lactation. However, the expert panel had advised that caution should be exercised until there was stronger evidence on the safety of *Echinacea* during lactation.

55. 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. Participants were matched with controls for age, alcohol use, and smoking. In this 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.

56. The Norwegian Mother and Child Cohort Study (Heitmann *et al*., 2016) investigated *Echinacea* use during pregnancy among 363 women (0.5% of participants) as part of a prospective population-based pregnancy cohort study. The most common reasons for *Echinacea* use were treatment of cold/flu, upper respiratory tract infections (including sinusitis, otitis, tonsillitis, and cough), lower respiratory tract infections (bronchitis and pneumonia), vaginal and oral herpes infections. *Echinacea* supplements were taken during early (206 women) and late (183 women) pregnancy, though timing details were incomplete, and dosage/preparation were unspecified. No increased risks were found for preterm birth, low birth weight, or small for gestational age. 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 users of *Echinacea* were hypospadias, cleft lip, and hypoplastic left heart syndrome.

57. In a 10-month study at maternity wards in Padua and Rovereto, Italy, using structured anonymous questionnaire, 27.8% of 392 women reported using herbal remedies during pregnancy (Cuzzolin *et al*., 2010). *Echinacea* was used orally by 10 women (9.2%) for colds, anxiety, and immune support. Details on species, dosage, and timing were not specified. By examining each herb separately, the authors reported that in one case there was a possible relationship between prolonged *Echinacea* intake and intrauterine growth restriction in a 35-week newborn. No further details were provided for that case.

58. A similar study aiming to investigate the use of herbal medicines in pregnant women in relation to pregnancy outcomes involved the administration of a structured questionnaire to 600 women within five days after delivery at Stavanger University Hospital Norway (Nordeng *et al*., 2011). 40% of women reported to have used herbal medicines during pregnancy, with *Echinacea* being used by 45 (7.5%) of those interviewed for cold and flu symptoms. No details were provided on *Echinacea* species, dosage, or timing. Birthweights were significantly higher among herbal users (mean 3,663 g vs. 3,508 g; p = 0.001), attributed to iron-rich herbs. No specific association between *Echinacea* use and birthweight or other outcomes was discussed.

Lactation

59. 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.

Adverse effects in humans

60. A meta-analysis of clinical trials (Schapowal *et al*., 2015) investigating the use of *Echinacea* in patients with respiratory tract infections looked at the adverse events recorded in the 6 clinical trials included in the analysis from a total of 1,440 *Echinacea*-treated subjects and 1,326 subjects receiving placebo. The studies used varying *Echinacea* preparations and doses. Four studies employed ethanol/glycerol extractions from *E. purpurea*/*E. angustifolia* (500–4,000 mg extract/day), and two used pressed juices from *E. purpurea* (6,200–10,000 mg/day). Overall, 491 adverse events occurred with *Echinacea* in comparison to 474 with placebo, but there were no significant differences between the groups. Most adverse effects reported were gastrointestinal disturbances and were mild and transient. Only two severe adverse events (stridor) occurred with *Echinacea* and one (glandular fever, requiring hospitalisation) in the placebo group. There were no significant differences in clinical biochemistry associated with *Echinacea* use.

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

62. A systematic review summarised evidence of the safety of *Echinacea* based herbal medicinal products from 36 clinical studies, case reports, and spontaneous

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

63. 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, 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).

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

Duration of use

65. The EMA recommends 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). No scientific rationale has been provided for the limits on the duration of use. *Echinacea* preparations have been used for longer durations without any serious adverse effects as described below.

66. 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 involved the administration of 800 mg *E. purpurea* whole plant extract twice a day for 6 months to 50 patients (Vonau *et al*., 2001). The only side effects reported were nausea (n = 4) and diarrhoea (n = 2). 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 randomized, double-blind, placebo controlled trial involving 289 patients (n=100 for *E. angustifolia*, n=99 for *E. purpurea*, n=90 for placebo) for the prevention of respiratory tract infections (Melchart, 1998). The side effects reported included minor gastrointestinal symptoms, headache/dizziness, allergic reactions and were similar between treatment arm and placebo (Melchart, 1998).

67. The safety and efficacy of Echinaforce was tested in a large randomised, double-blind, placebo-controlled clinical trial for 4 months. 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 (Jawad *et al*., 2012).

Mechanism of action

68. The exact mechanism by which *Echinacea* preparations exert their beneficial effect on the treatment and prevention of common cold is not known. Antiviral, immunomodulatory and anti-inflammatory effects of *Echinacea* were demonstrated in *in vitro*, *in vivo* and human studies referenced in the section below. However, the relevance of the *in vitro* and *in vivo* effects of *Echinacea* to clinical efficacy is not known and exact pharmacodynamic mechanism cannot be established (EMA, 2014).

In vitro and in vivo studies

Antiviral effects

69. The *Echinacea* antiviral mechanism of action is not fully elucidated, but it is thought to be due to prevention of viral entry into the cells rather than inhibition of viral replication (Pleschka *et al*., 2009; Sharma *et al*., 2009), suggesting that

Echinacea treatment is effective only at the very early stages in the infection process (Pleschka *et al*., 2009). The use of different species, extraction methods and preparations make it difficult to attribute the antiviral activity of *Echinacea* to specific compounds. *Echinacea* has also been reported to inhibit the induction of pro-inflammatory cytokines IL-6, IL-8 and TNF-α *in vitro* (Sharma *et al*., 2009) and IL-10 and IFN-γ *in vivo* (Fusco *et al*., 2010), which can contribute to improved clinical outcomes of influenza infections by modulating the immune response (Fusco *et al*., 2010).

Immunomodulatory and anti-inflammatory effects

70. 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.

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

***Echinacea* preparation**	**Concentration or dose**	**Test system**	**Summary of immune system effects**	**Reference**
Fresh and dried juice from EchinaFresh (*E. purpurea)* standardized for a content of 2.4% soluble β-1,2-D-fructofuranosides.	0.05-10 µg/mL fresh juice and 0.01-10 µg/mL dried juice.	Human peripheral blood macrophages.	Statistically significant increase in the production of IL-1, TNF-α, IL-6 and IL-10 by the macrophages at all concentrations of *Echinacea.*	Burger *et al*., 1997
E. purpurea raw herb and root powders subjected to simulated digestion protocol in simulated gastric fluid.	5 – 320 µg/mL	RAW267.7 murine macrophages.	Dose dependent induction of TNF-α, NO, IL-1α, IL-1β, and IL-6 with *Echinacea* treatment comparable to the results achieved with the LPS positive control.	Rinninger *et al*., 2002
Plant parts extracted with aqueous ethanol, producing four different fractions with concentrations of chicoric acid, polysaccharide and alkylamides at basal level, 3, 20 and 50 times the basal level.	100 µL *via* oral gavage	Male Sprague-Dawley rats.	*Echinacea* fractions at 20 and 50 times the basal dose levels significantly increased the phagocytic index in alveolar macrophages compared to basal and 3 times basal level dose. TNF-α secretion from alveolar macrophages showed a dose-dependent rise with 3 and 20 times basal level doses. Similarly, spleen macrophages exhibited dose-dependent increases in TNF-α and IFN-γ release.	Goel *et al*., 2002
Commercially available *E. purpurea* extracts with a defined chemical composition of chicoric acid (3.045%), caftaric acid (1.575%), chlorogenic acid (0.065%), dodeca-2E, 4E, 8Z,	400 µg/mL	Bone marrow-derived dendritic cells (BMDCs) derived from femur and tibia of 6–8-week-old female C57BL/6 mice.	*Echinacea* treatment significantly increased percentage of CD40, CD80, CD83 and CD86 markers on BMDCs and increased the secretion of IFN-γ, IL-12, IL-10, and TGF-β1 by BMDCs.	Li *et al*., 2017

10E/Z-tetraenoic acid isobutylamide (1.635%)			Endocytosis of fluorescently labelled dextran reduced by *Echinacea* treatment, similar to results observed with LPS control.	
Dried, ground preparations of fresh *E. purpurea* herb homogenized, filtered and used fresh the same day.	0.001 to 1000 pg/mL	Human peripheral blood mononuclear cells (PBMC) from healthy patients or patients with chronic fatigue syndrome (CFS) or acquired immunodeficiency syndrome (AIDS).	Significant increase in the NK cell activity from healthy patients and those with CFS and AIDS was observed following *Echinacea* treatment in a concentration dependent manner. A similar concentration dependent response was observed for the antibody dependent cell-mediated cytotoxicity in all three patient groups following *E. purpurea* treatment.	See *et al*., 1997
E. purpurea dissolved in water and filtered to prepare a water soluble extract.	Concentrations up to 10 µg/mL	Human peripheral blood mononuclear cells (PBMC).	Increase in the NK-mediated cytotoxic activity was observed with *E. purpurea* treatment in a concentration dependent manner. *Echinacea* treatment reduced CD16 expression (frequency and intensity) by lymphocytes, while increasing CD69 expression within $CD16^+$ populations, with over 90% $CD16^+$ cells expressing CD69 at the highest concentration.	Gan *et al*., 2003
Ground *E. purpurea* aerial parts and freeze dried into a powder. The preparation contained cichoric and caftaric acids, as well as cynarin, but not alkylamide.	Concentrations of up to 250 µg/mL	Human T-cell line Jurkat E6-1.	*E. purpurea* induced a dose-dependent increase in IL-2 secretion and a five-fold rise of IFN-γ secretion by high-density T cells.	Fonseca *et al*., 2014
Alcohol extracts of *Echinacea*.	130 mg/kg bw/day by gavage	Eight-week-old male BALB/c mice	All three *Echinacea* species increased IFN-γ production in mitogen-stimulated splenocytes,	Zhai *et al*., 2007

E. purpurea contained chicoric acid and caftraic acid, no echinacoside. *E. angustifolia* contained echiancoside, cynarin, chlorogenic acid. *E. pallida* contained echinacoside, chlorogenic acid and caftaric acid.			suppressed IL-1β and TNF-α. In non-stimulated splenocytes, *E. purpurea* significantly increased IL-1β secretion. *E. purpurea* increased the percentage of $CD49^+$ and $CD19^+$ splenic cells, while *E. angustifolia* only increased $CD49^+$; *E. pallida* had no effect on either. Only *E. pallida* significantly enhanced NK cell cytotoxicity.	

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

Human Studies

72. A meta-analysis (Schapowal *et al*., 2015) of six randomised control trials (RCTs) reported that *Echinacea* significantly reduced the relative risk (RR) of recurrent respiratory tract infections (RR = 0.649; 95% CI: 0.545–0.774; $p < 0.0001$). In individuals with high susceptibility to recurrent respiratory tract infections (e.g., stress, smoking, poor sleep, low T4/T8 ratio), the risk reduction was greater (RR = 0.501; 95% CI: 0.380–0.661; $p < 0.0001$). *Echinacea* treatment also halved the incidence of complications such as pneumonia, sinusitis, and bronchitis (RR = 0.503; 95% CI: 0.384–0.658; $p < 0.0001$), with pneumonia showing the greatest reduction (64.9%). The study concluded that *Echinacea* is an effective option for the management of recurrent respiratory tract infections and their related complications and that people with presumed lower immune function and high susceptibility to infection may benefit most. The authors attributed the increased resistance to viral infections observed in the human studies to the reported immunomodulatory effects of *Echinacea* in *in vitro* and *in vivo* studies.

73. Melchart *et al*. (1995) summarized the results of five placebo-controlled, randomized studies investigating the immunomodulatory activity of *Echinacea* extracts in a total of 134 healthy volunteers (18 females and 116 males) aged 18–40 years. The primary outcome measure was the relative phagocytic activity of polymorphonuclear neutrophil granulocytes (PNG). Two studies reported a significant increase in PNG phagocytic activity with *Echinacea* compared to placebo, while the remaining three found no significant effect. Peripheral blood leukocyte

counts were unchanged across all studies. The review authors concluded that it was difficult to draw firm conclusions regarding *Echinacea*'s effect on PNG activity due to methodological differences in measuring phagocytosis, small sample sizes, and the absence of chemically defined, standardised *Echinacea* preparations.

74. A human study with 10 healthy subjects (5 male and 5 female) evaluated the immunomodulatory effect of a standardised *E. angustifolia* root extract (Polinacea) by measuring the mRNA and protein levels of the cytokines IL-2, IL-8, IL-6 and TNF-α in plasma samples (Dapas *et al*., 2014). The subjects took 10 mL, equal to 100 mg *E. angustifolia* root extract containing 4.7 mg/10 mL of echinacoside and 8.0 mg/10 mL of high molecular weight polysaccharides, daily for 4 weeks. The study reported upregulated expression levels of IL-2 and IL-8 and downregulation of the pro-inflammatory cytokines TNF-α and IL-6 following *Echinacea* treatment. The maximal differential gene expression for the cytokines was observed after 14 days of *Echinacea* treatment. The authors acknowledge the study limitations such as small sample size and the lack of comparison to other *Echinacea* preparations.

Contaminants

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

76. 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%, $p = 0.55$).

77. 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.

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

79. *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

80. *Echinacea* is not used as a food commodity on its own or in recipes for cooking, but there are tea and honey products, found from online sources, supplemented with *Echinacea* and *Echinacea* extracts (Appendix B, Table 7) and these could be consumed as part of the general diet. Data from the National Diet and Nutrition Survey (NDNS) (Bates *et al*., 2014, 2016, 2020; Roberts *et al*., 2018) on acute herbal and fruit tea consumption and honey among women of childbearing age (16-49 years) may provide an indicator of *Echinacea* intake from these foods during pregnancy. The acute consumption scenario is considered because *Echinacea* products are likely to be consumed for a short period of time during an episode of cold/flu during pregnancy. The NDNS does not provide data for pregnant or lactating women, so while data is based on women of childbearing age, this may not necessarily be representative of the maternal diet. It is also worth noting that some of the *Echinacea* containing tea products advise pregnant or lactating women to consult a healthcare professional prior to using the product. The *Echinacea*-containing honey states that it is suitable for pregnant or breastfeeding women, whilst the lozenges contain no warnings. Like tablets and capsules, lozenges are solid dosage forms, but they are specifically designed to dissolve or disintegrate slowly in the mouth and are formulated with a flavoured or sweetened base.

81. 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. 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)**	**97.5thpercentile (mL/person /day)**	**Mean (mL/kg/ bw/day)**	**97.5th percentile (mL/kg bw/day)**
364	520	1,500	8.0	23

*Rounded to 2 significant figures.
^Based on women of childbearing age (16-49 years).

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

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

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

*Rounded to 2 significant figures.
^Based on women of childbearing age (16-49 years).

83. *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.

84. The *Echinacea* products for oral use with THR from the MHRA include tablets, capsules, oral solutions, tinctures and oromucosal spray (Appendix B, Table 13). The most common are tablets and capsules containing dry extract of *E. purpurea* root, with daily doses of 143–429 mg (equivalent to 858–3,000 mg root). Preparations from dried pressed juice of *E. purpurea* herb provide 176–352 mg daily (equivalent to 3.5–9.8 g fresh herb). A comparison between the THR products and the EMA monographs in terms of species used, preparations and doses can be found in Table 14, Appendix B. There is no evidence to suggest that THR products and *Echinacea* food supplements are taken together during pregnancy, and the assumption is that this is unlikely, especially since the THR products advise against use in pregnancy in their patient information leaflets. In addition, the regulation of THR products is a remit of the MHRA and the *Echinacea* exposure from licensed herbal *Echinacea* products is therefore not considered in the combined exposure scenarios.

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

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

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

*Rounded to 2 significant figures.

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

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

*Rounded to 2 significant figures.

Risk Characterisation

86. 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.

87. *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 usually of a single-herb composition containing either pressed juice or extracts from fresh or dried/root herb with specified drug extract ratios (DER) and mg amounts of extract and corresponding herb equivalent are clearly indicated.

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

89. 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.

90. 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.

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

92. 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 (n=206) 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.

93. The human studies demonstrate that *Echinacea* is consumed during pregnancy for similar indications as in the general population including the treatment and prevention of cold and flu and respiratory tract infections such as sinusitis, tonsilitis, cough, bronchitis and pneumonia. The COT Members highlighted that the Holst *et al*. (2011) study reporting 4.3% of women using *Echinacea* during pregnancy was conducted between the months of November and February, which could lead to an overestimation due to increased incidence of cold and flu infections during the

winter months. The COT also noted that the transient exposure makes it difficult to determine the percentage of women using *Echinacea* during the different stages of pregnancy and what the implications of extrapolating from different types of studies are.

94. No evidence of genotoxicity has been observed with *E. purpurea* and *E. angustifolia* 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.

95. 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.

96. 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*. The monographs don't provide a scientific rationale for the short duration of use recommended. *Echinacea* has been used in clinical studies for durations up to 6 months at doses of 1,800 mg/day with minimal side effects such as nausea and diarrhoea (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, it can be assumed that if used during pregnancy, *Echinacea* products will be consumed short term for the treatment and relief of common cold symptoms.

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

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

99. 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 and all the THR products carry labels warning against the use of the product during pregnancy and lactation.

100. 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. One 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.

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

Conclusions

102. Three *Echinacea* species – *E. purpurea*, *E. angustifolia* and *E. pallida* have been used medicinally to relieve the symptoms and shorten the duration of cold and flu infections. *Echinacea* preparations can be made from the dried roots of all three species, the fresh or dried aerial parts and the pressed juice from *E. purpurea*. Ethanolic extracts are also often used in many *Echinacea* products. The effects of *Echinacea* are due to the combination of bioactive metabolites including alkylamides, caffeic acid derivatives and polysaccharides. The composition of these compounds varies across the species, the plant parts, season, growing conditions and extraction methods used.

103. There is evidence from *in vitro* and *in vivo* studies that *Echinacea* preparations can inhibit the entry of influenza virus in the cells and modulate the immune response after a viral infection. Clinical studies suggest that *Echinacea* can lower the risk of recurrent respiratory tract infections and complications that arise from them. There are herbal products containing *E. purpurea*, *E. angustifolia* and *E. pallida* that have herbal medicinal licences in EU/EEA member states and THR licenses from the MHRA based on traditional use for the relief of common cold symptoms. These products are licensed for adults and children over 12 years of age and not recommended for pregnant or lactating women due to insufficient safety data available. Nevertheless, data from surveys on the use of herbal medicines during pregnancy suggests that up to 10% of pregnant women may use *Echinacea* for the treatment and prevention of cold/flu and immune system support.

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

105. 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 two human studies investigating the effects of *Echinacea* on pregnancy outcomes and they did not highlight any adverse effects associated with gestational use of *Echinacea*. These studies are observational and rely on self-reported use of *Echinacea* during pregnancy. The dose, preparation or duration of use were not reported.

106. 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.

107. 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 the 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.

108. 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.

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

110. Overall, the Committee considered the risk to maternal health from *Echinacea* exposure during pregnancy likely to be low but highlighted that there was insufficient information to enable a robust risk assessment and derive any health-based guidance values.

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

ICP-MS	Inductively-coupled plasma mass spectrometer
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
INF	Inteferon
IV	Intravenous
LDH	Lactate dehydrogenase
LU	Lytic units
MAPK	Mitogen-activated protein kinase
MDCK	Madin-Darby canine kidney cells
MHRA	Medicines and Healthcare Products Regulatory Agency
MN	Micronuclei
MNPCE	Micronucleated polychromatic erythrocytes
NHANES	National Health and Nutrition Examination Survey
NCE	Normochromatic erythrocytes
NDNS	National Diet and Nutrition Survey
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK cells	Natural killer cells
OECD	Organisation for Economic Co-operation and Development
PBMC	Peripheral blood mononuclear cells
PCE	Polychromatic erythrocytes
PFU	Plaque-forming unit
P-gp	P glycoprotein
PMN	Polymorphonuclear leukocytes
PNG	Polymorphonuclear neutrophil granulocytes
RBCs	Red blood cells
RET	Reticulocytes
RPMI	Roswell Park Memorial Institute
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SHE	Syrian hamster embryo cells
SMA	Smooth muscle antibodies

STP	Skin prick testing
TGF-β1	Transforming growth factor beta
THR	Traditional herbal registration
TNF	Tumour necrosis factor
TTP	Thrombotic thrombocytopenic purpura
UKTIS	UK Teratology Information Service
VEGF	Vascular endothelial growth factor
WBC	White blood count
WHO	World Health Organization

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TOX/2025/45 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.

TOX/2025/45 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**	***Echinacea* species and plant part**	**Composition**	**Directions for use**	**Daily dose of *Echinacea* (mg)**	**Additional information/ warnings**
Pukka Herbs | Elderberry and Echinacea Organic Herbal Tea	Tea bags.	*Echinacea* (species not specified) herb.	Ginger root, liquorice root, ***Echinacea* 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, ***Echinacea***, 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

Yogi Tea, Echinacea Immune Support, Caffeine Free, 16 Tea Bags, 0.85 oz (24 g)	Tea bags.	*Echinacea purpurea* Plant part not specified.	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).	Bring water to boiling and steep 7 minutes. For a stronger tea, use 2 tea bags. Drink 3-4 cups daily.	432 - 1,152 mg *Echinacea purpurea* and 141 - 376 mg *Echinacea purpurea* extract.	Consult your healthcare provider prior to use if you are pregnant or nursing, taking any medication or if you have a medical condition.
Traditional Medicinals, Organic Echinacea Plus, Elderberry, Caffeine Free, 16 Wrapped Tea Bags, 0.85 oz (24 g)	Tea bags.	*Echinacea purpurea* herb.	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).	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.	5,025 - 6,030 mg *Echinacea purpurea* herb.	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.

Traditional Medicinals, Organic Immune Zoom®, Lemon Ginger Echinacea, Caffeine Free, 16 Wrapped Tea Bags, 1.13 oz (32 g)	Tea bags.	*Echinacea purpurea* roo.t	2,000 mg herb blend (ginger rhizome, ***Echinacea purpurea* herb**, lemon myrtle leaf (*Backhousia citriodora*), lemon peel, liquorice root, peppermint leaf, ***Echinacea purpurea* root dry extract** (2-8:1), cardamom seed, Organic liquorice root dry extract (6:1).	Pour 8 oz (~227 mL) freshly boiled water over 1 tea bag. Cover & Steep for 10-15 min. Enjoy 2 cups throughout the day.	Not specified.	Consult your healthcare practitioner prior to use if you are pregnant or breastfeeding; or if you have an autoimmune or other immune 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.	*Echinacea* (species not specified) root.	Green tea (26%), Ginger root (15%), White hibiscus, Cinnamon bark, Natural lemon Flavouring with other Natural Flavourings (10%), ***Echinacea* 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 Echinacea Angustifolia Root	Loose herb for tea.	*Echinacea angustifolia* 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 Echinacea Wellness Tea, 16 oz	Loose herb for tea.	*Echinacea purpurea* herb and root.	Elderberry, ***Echinacea purpurea* herb**, peppermint, yarrow, ginger, chamomile flower, *Echinacea purpurea* root.	Pour 8 oz. (227 mL) boiling water over 1 tablespoon of tea. Cover and steep 10-15 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, Cut & Sifted Echinacea Purpurea Herb	Loose herb for tea.	*Echinacea purpurea* herb.	One teaspoon contains 820 mg *Echinacea purpurea* 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 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	*Echinacea purpurea* 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	*Echinacea* (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 & Echinacea, Orange & Lemon, 60 Lozenges	Lozenges	*Echinacea purpurea* herb (aerial parts) powder.	Each lozenge contains: 100 mg vitamin C, 25 mg zinc, **20 mg *Echinacea purpurea* powder**, 20 mg elderberry extract.	As a dietary supplement, dissolve one lozenge in the mouth two times per day.	40 mg *Echinacea purpurea* powdered herb.	NA

Table 8: *Echinacea* food supplements (solid dosage forms).

Product name	**Dosage form**	***Echinacea* species and plant part**	**Composition**	**Directions for use**	**Daily dose *Echinacea* (mg)**	**Additional information**
NOW Foods Echinacea 400 mg 100 Veg Capsules	Capsules	*Echinacea purpurea* 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	*Echinacea* (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.
Swanson Echinacea, 400mg herbal supplement	Capsules	*Echinacea purpurea* 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	*Echinacea purpurea* 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	*Echinacea purpurea* herb and *Echinacea angustifolia* root.	*Echinacea purpurea* (aerial parts) extract 125 mg [standardised to 4% phenolic compounds]. *Echinacea angustifolia* (root) extract 125 mg [standardised to 4% echinacosides].	Take 1 capsule twice daily.	250 mg *Echinacea purpurea* (aerial parts) extract and 250 mg *Echinacea angustifolia* (root) extract.	Consult with your physician if you are undergoing treatment for a medical condition or if you are pregnant or lactating.
Specialist Herbal Supplies (SHS)	Capsules	*Echinacea angustifolia*.	325 mg. Preparation not specified.	1 capsule, 3 times a day, taken with food or a drink. If desired,	975-1,300 mg *Echinacea angustifolia*.	If you are pregnant, breast-feeding, have a medical condition or are under

Echinacea Capsules				up to four times this amount can safely be taken.		medical supervision, please consult a doctor before use.
Nuke Nutrition Echinacea Tablets High Strength x180 - Immune Support Echinacea Herbal Supplements	Tablets	*Echinacea*. Species and part of plant not specified.	200 mg extract (DER 10:1) equivalent to 2,000 mg *Echinacea*.	Take 1 tablet with your first meal of the day.	200 mg extract equivalent to 2,000 mg *Echinacea.*	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	*Echinacea purpurea.* Plant part not specified.	350 mg extract (DER 10:1) equivalent to 3,500 mg *Echinacea pupurea*.	Take 1 capsule per day with water.	350 mg extract equivalent to 3,500 mg *Echinacea purpurea*.	NA
Nature's Way, Echinacea Goldenseal, 450 mg, 100 Vegan Capsules	Capsules	*Echinacea purpurea* herb (aerial parts) and *Echinacea angustifolia* root.	450 mg *Echinacea* 7 Herb Blend: ***Echinacea purpurea* (stem, leaf, flower)**, Goldenseal (root), ***Echinacea angustifolia* (root)**, Burdock (root), Gentian (root), Cayenne Pepper (fruit), Wood Betony (stem, leaf, flower)	Take 2 capsules twice daily, preferably with food.	1,800 mg *Echinacea* 7 herb blend. Exact dose of *Echinacea* cannot be determined.	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.
Nature's Way, Echinacea Purpurea Herb,	Capsules	*Echinacea purpurea* herb (aerial parts).	400 mg herb.	Adults take 3 capsules three times daily, preferably with food.	3,600 mg herb.	If pregnant, nursing, or taking any medications,

1,200 mg, 180 Vegan Capsules (400 mg per Capsule)				Only take this supplement if they are suffering severe illness to stimulate the immune system and to not take for longer than 5 days.		consult a healthcare professional before use.
California Gold Nutrition, EuroHerbs, Echinacea Herb Extract, Euromed Quality, 80 mg, 180 Veggie Capsules	Capsules	*Echinacea purpurea* herb (aerial parts).	80 mg *Echinacea purpurea* (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	*Echinacea purpurea* herb and *Echinacea angustifolia* root.	125 mg *Echinacea* blend (*Echinacea purpurea* herb extract and *Echinacea angustifolia* root powder)	Adults take two (2) capsules daily with any meal or as directed by a healthcare provider.	250 mg *Echinacea* blend (*Echinacea purpurea* herb extract & *Echinacea angustifolia* 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	*Echinacea purpurea* herb (aerial parts).	400 mg *Echinacea purpurea* 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	*Echinacea purpurea* root, aerial parts and seed and *Echinacea angustifolia* root.	800 mg Proprietary Extract Blend: ***Echinacea purpurea* root**, Goldenseal (Hydrastis canadensis) root, ***Echinacea angustifolia* root**, ***Echinacea purpurea* seed**, St. John's Wort (*Hypericum perforatum*) aerial parts, ***Echinacea purpurea* aerial parts**	Adults take 2 capsules 3 times daily between meals.	4,800 mg Proprietary Extract Blend. Exact dose of *Echinacea* cannot be determined.	Not for use during pregnancy or lactation.
Specialist Herbal Supplies (Shs) Echinacea Compound	Capsules	*Echinacea angustifolia*	*Echinacea angustifolia* 92mg, Garlic 92mg, Myrrh 92mg, Wild Indigo 46mg. *Echinacea* preparation not specified.	1 capsule, 3 times a day, taken with food or a drink.	276 mg *Echinacea angustifolia.*	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.

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

Product name	**Dosage form**	***Echinacea* species and plant part**	**Composition**	**Directions for use**	**Daily dose *Echinacea* (mg)**	**Additional information**
Nature's Way, Echinacea, 500 mg, 1 fl oz (30 mL)	Oral solution.	*Echinacea purpurea* 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	Adults: 500-1,500 mg herb extract Children: 250-750 mg herb extract.	If pregnant, nursing, or taking any medications, consult a healthcare professional

				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.		before use. Not recommended for individuals with auto-immune conditions.
Echinacea Single Herbal Tincture 150mL	Tincture	*Echinacea* (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 (angustifolia) Herbal Tincture	Tincture	*Echinacea angustifolia*.	Herb:Liquid 1:3.	No guidance.	No guidance.	NA
Napiers the Herbalists Napiers Organic Echinacea Drops	Oral drops	*Echinacea purpurea* 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 1-2 mL solution.	Not suitable for children under 12 years. Do not take if pregnant or breastfeeding.
100% Organic Echinacea Tincture Viridian 50ml	Tincture	*Echinacea purpurea* 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	*Echinacea angustifolia* and *Echinacea purpurea* root.	Root extract. 1.6 mL per 2 droppersfuls.	Take 1 to 2 droppersful in tea or water 1 to 3	0.8 - 4.8 mL.	Not recommended

				times daily as needed. Continuous high-level consumption of this product for more than 2 weeks of each month is not recommended.		for pregnant or nursing women.
Cytoplan Organic Echinacea	Oral solution	*Echinacea angustifolia*	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.

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)	**Estimated exposure to *Echinacea* (mg/day)**	**Estimated exposure to *Echinacea* (mg/day)**	**Estimated exposure to *Echinacea* (mg/day)**	**Estimated exposure to *Echinacea* (mg/day)**	**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)	**Estimated exposure to Echinacea (mg/day)**	**Estimated exposure to Echinacea (mg/day)**	**Estimated exposure to Echinacea (mg/day)**	**Estimated exposure to Echinacea (mg/day)**	**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
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)	**Estimated exposure to Echinacea (mg/day)**	**Estimated exposure to Echinacea (mg/day)**	**Estimated exposure to Echinacea (mg/day)**	**Estimated exposure to Echinacea (mg/day)**	**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.

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

Product name	**Dosage form**	***Echinacea* species and plant part**	**Composition**	**Directions for use**	**Daily dose *Echinacea* (mg)**
Echinaflu Soft Capsules	Capsules	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea pallida* (Nutt.) Nutt. root and *Echinacea purpurea* (L.) Moench root.	200mg of *Echinacea pallida*. Nutt. and 200mg of *Echinacea purpurea* (L.) Moench powedered root.	1 capsule twice a day for no longer than 10 days.	400 mg *E. pallida* powdered root and 400 mg *E. purpurea* powdered root. Total of 1,600 mg powdered root.
Solgar Echinacea Cold and Flu Capsules	Capsules	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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.

Echinaforce Forte Cold & Flu Tablets	Tablets	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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.

Cold-n-Flu-Eze					
Fuerte Tablets	Tablets	Wild indigo root (*Baptisia tinctoria* (L.) R.Br.), ***Echinacea purpurea* root (*Echinacea purpurea* (L.) Moench), *Echinacea pallida* root (*Echinacea pallida* (Nutt.) Nutt.)**, White cedar tips and leaves (*Thuja occidentalis* L.)	3.2 mg dry root extract (DER 4-9:1) from Wild indigo root, *E. purpurea root*, *E. pallida 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 *E. pallida* and 9.2 mg *E. purpurea* 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	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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.

Potter's Skin Clear Tablets	Tablets	*Echinacea angustifolia* (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.
EKINACLEAR	Tablets	*Echinacea purpurea* (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	*Echinacea purpurea* (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.	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (L.) Moench herb, Uva-ursi herb (*Arctostaphylos uva-ursi* (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	*Echinacea angustifolia* (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.

Echinacin Juice MADAUS	Oral solution	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (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	*Echinacea purpurea* (L.) Moench herb and root, Sage leaves, (*Salvia officinalis L. folium*).	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	*Echinacea purpurea* (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).

[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.

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

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