

# Annex A to TOX/2025/45

Annex A to TOX/2025/45

## Introduction and Background

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## Introduction

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

health project Annex (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 ketoalkenyne (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.

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## **Pharmacokinetic studies**

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22. The EMA assessment reports on *E. purpurea* (EMA, 2014) and *E. angustifolia* (EMA, 2012) note that available pharmacokinetic data are limited and primarily focus on alkylamides and, to a lesser extent, caffeic acid conjugates. According to the human pharmacokinetic studies reviewed in the EMA reports, the alkylamides from *E. purpurea* and *E. angustifolia* show good oral bioavailability with rapid absorption and measurable plasma concentration within 20-60 minutes post-ingestion. The reported peak plasma concentration C<sub>max</sub> 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<sub>max</sub> 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*.

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# **Drug-herb interaction potential: effects on cytochrome P450 and P-glycoprotein**

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

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

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# Toxicity Studies

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# **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 LD50 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 LD50 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  $\geq 150$  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	<i>Echinacea</i> 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)
Chow <i>et al.</i> 2006	Animal study (DBA/2 mice)	<i>E. purpurea</i> extract 0.45 mg/kg bw/day (dose per body weight)	Not covered	Covered	Covered	Covered
Barcz <i>et al.</i> 2007	Animal study (Balb/c mice)	<i>E. purpurea</i> extract 0.6 mg/day	Not covered	Covered	Covered	Covered
Khaksary Mahabady <i>et al.</i> , 2006	Animal study (NMRI mice)	<i>E. purpurea</i> extract 360 mg/kg	Not covered	Covered	Covered	Covered
Maass <i>et al.</i> , 2005)	Animal study (pigs)	<i>E. purpurea</i> dried cobs 0.5-3.6%	Not covered	Not covered	Not covered	Covered
Dabbou <i>et al.</i> , 2016	Animal study (rabbits)	<i>E. pallida</i> 3 g/kg	Not covered	Covered	Covered	Covered

Kovitvadhi <i>et al.</i> , 2016	Animal study (rabbits)	<i>E. pallida</i> 3 g/kg	Not covered	Not covered	Not covered	Not covered
Gallo <i>et al.</i> , 2000	Human prospective controlled study	<i>E. purpurea</i> and <i>E.</i> <i>angustifolia</i> 250- 1000 mg/day	Unknown	Covered	Covered	Covered
Heitmann <i>et al.</i> , 2016	Human prospective cohort study	Not known	Unknown	Covered	Covered	Covered
Cuzzolin <i>et al.</i> , 2010	Human cross- sectional study	Not known	Unknown	Unknown	Unknown	Unknown
Nordeng <i>et al.</i> , 2011	Human cross- sectional study	Not known	Unknown	Unknown	Unknown	Unknown
Matthias <i>et al.</i> , 2008	Human case report	Four tablets each containing <i>E.</i> <i>purpurea</i> 675 mg and <i>E.</i> <i>angustifolia</i> 600 mg	Not covered	Not covered	Not covered	Not covered

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

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 fetuses, 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

**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%

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 Ec

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.

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

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 G

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# Duration of use

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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  $\geq 2$  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).

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## Mechanism of action

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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- $\alpha$  *in vitro* (Sharma *et al.*, 2009) and IL-10 and IFN- $\gamma$  *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- $\alpha$  (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- $\gamma$  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.

<b><i>Echinacea</i> preparation</b>	<b>Concentration or dose</b>	<b>Test system</b>	<b>Summary of immune system effects</b>	<b>Reference</b>
Fresh and dried juice from EchinaFresh ( <i>E. purpurea</i> ) standardized for a content of 2.4% soluble β-1,2-D-fructofuranosides.	0.05-10 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 <i>Echinacea</i> .	Burger <i>et al.</i> , 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  $\mu$ L *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- $\alpha$  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- $\alpha$  and IFN- $\gamma$  release.

Goel *et al.*, 2002

Commercially available *E. purpurea* extracts with a defined chemical composition of chicoric acid (3.045%), caftaric acid (1.575%), chlorogenic acid (0.065%), dodeca-2E, 4E, 8Z, 10E/Z-tetraenoic acid isobutylamide (1.635%)

400 µg/mL

Bone marrow-derived dendritic cells (BMDCs) derived from femur and tibia of 6–8-week-old female C57BL/6 mice.

*Echinacea* treatment significantly increased percentage of CD40, CD80, CD83 and CD86 markers on BMDCs and increased the secretion of IFN-γ, IL-12, IL-10, and TGF-β1 by BMDCs. Li et al., 2017

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

Increase in the NK-mediated cytotoxic activity was observed with *E. purpurea* treatment in a concentration dependent manner.

*Echinacea* treatment

*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).

reduced CD16 expression

Gan *et al.*, 2003

(frequency and intensity) by lymphocytes,

while increasing

CD69 expression

within CD16<sup>+</sup> populations,

with over 90% CD16<sup>+</sup> cells

expressing CD69 at the

highest concentration.

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

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- $\alpha$  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- $\alpha$  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.

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# Contaminants

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

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# Exposure Assessment

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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.<sup>81</sup> The consumption of herbal and fruit tea (as consumed), as a proxy for *Echinacea* tea consumption (without recipes).

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).

<b>Consumers (n)<sup>^</sup></b>	<b>Mean (mL/person /day)</b>	<b>97.5<sup>th</sup> percentile (mL/person /day)</b>	<b>Mean (mL/kg/bw/day)</b>	<b>97.5<sup>th</sup> percentile (mL/kg bw/day)</b>
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 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).

<b>Consumers (n)^</b>	<b>Mean (g/person /day)</b>	<b>97.5<sup>th</sup> percentile (g/person /day)</b>	<b>Mean (g/kg/ bw/day)</b>	<b>97.5<sup>th</sup> percentile (g/kg bw/day)</b>
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.

<b>Echinacea containing food/food supplement</b>	<b>Estimated exposure to <i>Echinacea</i> (mg/day)</b>
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.

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

\*Rounded to 2 significant figures.

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## Risk Characterisation

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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, tonsillitis, cough, bronchitis and pneumonia. The COT Members highlighted that the Holst *et al.* (2011) study reporting 4.3% of women using *Echinacea* during pregnancy was conducted between the months of November and February, which could lead to an overestimation due to increased incidence of cold and flu infections during the winter months. The COT also noted that the transient exposure makes it difficult to determine the percentage of women using *Echinacea* during the different stages of pregnancy and what the implications of extrapolating from different types of studies are.

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.

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## **Conclusions**

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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.

Annex A to TOX/2025/45

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ACAH	Acute cholestatic autoimmune hepatitis
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reactions
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
bFGF	Basic fibroblast growth factor
BMDCs	Bone marrow derived dendritic cells
bw	Body weight
CAM	Complementary and alternative medicines

CFS	Chronic fatigue syndrome
CFU	Colony forming units
CI	Confidence intervals
CYP	Cytochrome P450
DER	Drug extract ratio
DTAI	Dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides
EFSA	European Food Standards Agency
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicine Agency
FCV	Feline calicivirus
FDA	Food and drug administration
GLP	Good laboratory practice
GHS	Globally Harmonized Classification System
HBGV	Health-based guidance values
HMR	Human Medicines Regulation
HMPC	Committee on Herbal Medicinal Products

HPLC	High performance liquid chromatography
HPRT	Hypoxanthine phosphoribosyltransferase
HSV	Herpes simplex virus
ICP-MS	Inductively-coupled plasma mass spectrometer
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
INF	Inteferon
IV	Intravenous
LDH	Lactate dehydrogenase
LU	Lytic units
MAPK	Mitogen-activated protein kinase
MDCK	Madin-Darby canine kidney cells
MHRA	Medicines and Healthcare Products Regulatory Agency
MN	Micronuclei
MNPCE	Micronucleated polychromatic erythrocytes

NHANES	National Health and Nutrition Examination Survey
NCE	Normochromatic erythrocytes
NDNS	National Diet and Nutrition Survey
NF- $\kappa$ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK cells	Natural killer cells
OECD	Organisation for Economic Co-operation and Development
PBMC	Peripheral blood mononuclear cells
PCE	Polychromatic erythrocytes
PFU	Plaque-forming unit
P-gp	P glycoprotein
PMN	Polymorphonuclear leukocytes
PNG	Polymorphonuclear neutrophil granulocytes
RBCs	Red blood cells
RET	Reticulocytes
RPMI	Roswell Park Memorial Institute
RSV	Respiratory syncytial virus

## SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus-2

SHE	Syrian hamster embryo cells
SMA	Smooth muscle antibodies
STP	Skin prick testing
TGF- $\beta$ 1	Transforming growth factor beta
THR	Traditional herbal registration
TNF	Tumour necrosis factor
TTP	Thrombotic thrombocytopenic purpura
UKTIS	UK Teratology Information Service
VEGF	Vascular endothelial growth factor
WBC	White blood count
WHO	World Health Organization

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