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 ketoalkenynes (EMA, 2018). The herbal preparation for traditional use consists of dry extract (DER 4-8:1) or tincture (ratio of herbal substance to extraction solvent 1:5), both obtained with 50% v/v ethanol extraction solvent (EMA monograph, 2018).

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

19. *E. purpurea* is on the Community list of herbal substances, herbal preparations and combinations thereof for traditional medicinal products based on traditional topical use for the treatment of small superficial wounds (HMPC, 2007). The benefit-risk assessment, conducted by EMA, concluded that there was sufficient clinical evidence to support the well-established medicinal use, in

accordance with Directive 2001/83/EC, of expressed juice preparations from *E. purpurea* fresh herb for the short-term prevention (maximum 10 days) and treatment of common cold in adults and children over the age of 12 (EMA, 2014).

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

Health-based guidance values (HBGVs)

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