Risk Characterisation

In this guide

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

87. *Echinacea* products are available as foods (Appendix B, Table 7), supplements (Appendix B, Tables 8-9) and as traditional herbal medicinal

products with THR from the MHRA (Appendix B, Table 13). *Echinacea* food supplements and products with THR share some similarities such as the species (predominantly *E. purpurea* and *E. angustifolia*) and use of dosage forms such as capsules, tablets and tinctures. The THR products are usually of a single-herb composition containing either pressed juice or extracts from fresh or dried/root herb with specified drug extract ratios (DER) and mg amounts of extract and corresponding herb equivalent are clearly indicated.

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

89. The COT agreed there was a lack of high-quality available data on the reproductive end points from both animal and human studies. None of the animal studies available on the reproductive and developmental effects of Echinacea conform to the OECD guidelines. A potential data gap identified by the Committee was the absence of studies looking at the placenta and the maintenance of pregnancy. It was highlighted that identifying these data gaps is particularly important given the recommended short-term use of Echinacea leading to a transient exposure window during the different parts of the reproductive and developmental cycle.

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

91. The COT highlighted that small numbers of animals were used in both mice studies with only one dose of *Echinacea* tested. In addition, the COT

Members were not convinced by the conclusion reached by Chow *et al*. (2006) stating that *Echinacea* could lead to miscarriages in early pregnancy as the study had used a DBA mouse strain with small litter size and the range/standard deviation for the foetal loss results were not provided.

92. No interventional clinical trials exist on *Echinacea* use during pregnancy or lactation (EMA, 2014). Limited human data from observational studies (Gallo *et al*., 2000; Heitmann *et al*., 2016) and surveys (Cuzzolin *et al*., 2010; Nordeng *et al*., 2011) show no adverse maternal or infant effects specifically linked to *Echinacea*. Both observational studies (Gallo *et al*., 2000; Heitmann *et al*., 2016) reported no significant differences in malformations, birth weight, or pregnancy outcomes between exposed and control groups. The COT commented that the sample size (n=206) in the study by Gallo *et al.* (2000) would not give sufficient statistical power to detect the birth defects and malformations studied. The COT also highlighted that the limited human studies on the use of *Echinacea* during pregnancy focus on observations that can be detected at birth and did not consider any longer-term effects such as epigenetic changes.

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

94. No evidence of genotoxicity has been observed with *E. purpurea* and *E. angustifolia* preparations in *in vitro* bacterial reverse mutation assays, *in vitro* chromosomal aberration tests as well as *in vivo* micronucleus test conducted by several OECD guideline conforming studies. The animal data from studies investigating the acute, subacute and sub-chronic toxicity of *Echinacea* suggest that overall *Echinacea* has low toxicity and is well tolerated. Upon reviewing the data from human studies on *E. purpurea,* EMA (2014) concluded that oral preparations are well tolerated and have an acceptable safety profile with mild, transient and reversible adverse effects, with gastrointestinal disturbances and

allergic skin reactions being the most commonly reported adverse effects.

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

96. The Echinacea products with THR recommend a duration of use no longer than 10 days. This is in line with the EMA monographs on E. purpurea, E. angustifolia and E. pallida. The monographs don’t provide a scientific rationale for the short duration of use recommended. Echinacea has been used in clinical studies for durations up to 6 months at doses of 1,800 mg/day with minimal side effects such as nausea and diarrhoea (Vonau et al., 2001). Doses of 2,400-4,000 mg daily were also well tolerated in a 4 month long study with 755 participants (Jawad et al., 2012). Given the indications for Echinacea use and the warnings on most products to avoid prolonged use, it can be assumed that if used during pregnancy, Echinacea products will be consumed short term for the treatment and relief of common cold symptoms.

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

(1,600 mg/day for 28 days) showed no significant CYP changes (Gurley, 2004). Overall, Echinacea has the potential to interact with medications, but clinical evidence remains limited.

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

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

100. The estimated exposures to *Echinacea* by the FSA Exposure assessment team (EAT) range between 400 – 3,600 mg from food supplements (oral liquids, tablets, capsules), 19-100 mg from honey and 860 – 6,000 mg from tea products. If a combination of food and food supplement products are taken, exposure levels can reach up to 13,000 mg/day. *Echinacea* doses used in clinical studies vary between 100-4,000 mg/day extract and 6,200-10,000 mg/day pressed juice with duration from 5 days to 4 months, with *E. purpurea* and *E. angustifolia* being the most commonly used. One caveat is that the exposures estimated by the EAT team are based on dried *Echinacea* root/herb rather than extracts/pressed juice as many of the supplements and food products either list the *Echinacea* content as dried plant parts or do not specify the nature of the preparation. Thus, a direct comparison is challenging as generally extracts are more concentrated and potent than the dried plant equivalents.

101. Overall, the COT agreed that the human studies available lack information about the specific *Echinacea* species, plant part, type of preparation used, administered dose, the duration of intake and the trimester during which *Echinacea* was used. It is therefore not possible to directly compare doses used

during pregnancy in ‘real life’ situations to exposures estimated by the FSA EAT team. In addition, the COT agreed that the point of departure for *Echinacea* to be used in risk assessments was difficult to derive due to complexity in terms of preparations, extracts, doses and lack of sufficient, high-quality data to determine clear safety risks.