Risk Characterization

In this guide

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156. 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.

157. The 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 most commonly used. These doses are comparable to those estimated by the FSA Exposure Assessment Team (EAT) for Echinacea consumption from different supplements and foods during pregnancy. One caveat is that the doses 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.

158. There are limited data from animal and human studies on the safety of Echinacea use during pregnancy and lactation. None of the animal studies available on the reproductive and developmental effects of Echinacea conform to the OCED guidelines. 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 and some conflicting results on angiogenic activity, whereby one of the preparations increased angiogenic activity, another decreased it and the third one had no effect. The study concluded that Echinacea may influence foetal angiogenesis and should be avoided during pregnancy as a precaution. Small numbers of animals were used in both studies and only one dose of Echinacea was tested. A mice study by Khaksary Mahabady et al. (2006) suggested that E. purpurea extracts can reduce the incidence of phenytoin induced cleft palate.

159. A study examining the effects of E. purpurea in pregnant pigs (Maass et al., 2005) found no significant differences in the biochemical and immunological parameters of the sows and reported no adverse effects in the piglets. Another study looking at E. pallida supplementation in pregnant rabbits found no significant effects on the reproductive, haematological or immune parameters of the does (Dabbou et al., 2016). The second part of the study (Kovitvadhi et al., 2016) investigated the effects of Echinacea supplementation on the offspring and reported no significant differences in growth performance, blood biochemistry or humoral immune response between rabbits born to Echinacea treated and control group does.

160. There are no prospective interventional clinical trials on Echinacea use in pregnant or lactating women (EMA, 2014). There is a prospective controlled study (Gallo et al., 2000) and a cohort study (Heitmann et al., 2016) looking at pregnancy outcomes associated with Echinacea use. There are two studies administered through self-reported surveys aiming to investigate the use of herbal remedies, including Echinacea, in pregnant women and link them to pregnancy outcomes. (Cuzzolin et al., 2010; Nordeng et al., 2011). The limited data from the human studies did not reveal any adverse effects on the mother or the infant that are specifically linked to Echinacea use during pregnancy. The two observational studies by Gallo et al. (2000) and Heitmann et al. (2016) reported no significant differences in the rates of malformations, birth weight and pregnancy outcomes between treatment and control groups.

161. 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. Overall, 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 those estimated by the FSA EAT team.

162. 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 Echinacea 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. A systematic review on the adverse effects of Echinacea found that they were most frequently associated with ethanolic herb and root extracts (Di Lorenzo et al., 2015).

163. There are case reports in the literature and pharmacovigilance databases suggesting that Echinacea can be associated with serious allergic reactions, including anaphylaxis, particularly in patients with history of atopy. A study by Mullins and Heddle (2002) looked at potential IgE-mediated hypersensitivity reactions identified from the Australian Adverse Drug Reactions Advisory Committee's database and evaluated five of the patients, who had suffered anaphylaxis, asthma attacks or macular rash after Echinacea exposure. The study concluded that patients with history of atopic diseases should be cautioned against Echinacea use due to possible cross-reactivity between Echinacea and other allergens. EMA (2014) also recommends that atopic patients should consult their doctor before using Echinacea.

164. There are isolated case reports of Echinacea triggering autoimmune diseases such as erythema nodosum, hyperoesinophilia, leucopenia, thrombocytopenia, severe acute cholestatic autoimmune hepatitis and fatal liver necrosis. EMA has reviewed these case reports and 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 highlights that infectious agents and inflammatory processes present in common cold can promote autoimmune diseases.

165. 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.

166. Most commercially available Echinacea preparations, both food supplements and products with THR, warn against use in people with autoimmune conditions. EMA also states 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). There is a body of evidence from in vitro, in vivo and human studies that Echinacea has immunomodulatory properties, which are in part responsible for its effects on lowering the risk of recurrent respiratory tract infections, their complications and alleviating the symptoms of influenza infections. An in vivo mice study by Fusco et al. (2010) suggested that treatment with Echinacea improved the clinical outcomes of influenza infected mice due to immune system modulation and decrease in serum IFN-γ and IL-10 brought by Echinacea. The effects of Echinacea on cytokine production by the immune system are complex. Echinacea was effective at inhibiting the induction of IL-6, IL-8 and TNF-α in human cell lines infected with influenza, rhinovirus, adenovirus and respiratory syncytial virus (Sharma et al., 2009). On the other hand, Echinacea has been shown to stimulate TNF-α, IL-1α, IL-1β production from macrophages in a similar way to bacterial LPS in vitro (Burger et al., 1997; Rininger et al., 2002). A study in rats (Goel et al., 2002) showed that Echinacea stimulates phagocytosis in alveolar macrophages and release of TNF-α and IFN-γ release by spleen macrophages, whilst the results of an in vivo mice study suggested that Echinacea treatment decreases the production of IL-1β and TNF-α by LPS stimulated macrophages (Zhai et al., 2007). Zhai et al. (2007) also reports that treatment with E. angustifolia and E. pallida increases the production of TH2 cytokines (IL-4, IL-6, and IL-10) by splenic lymphocytes, suggestive of anti-inflammatory activity.

167. Studies have also demonstrated that Echinacea can activate NK mediated cytotoxicity in vitro (Gan et al., 2003; See et al., 1997) and in vivo (Zhai et al., 2007). The study by Chow et al. (2006), investigating the link between maternal Echinacea consumption and spontaneous abortions in mice, was based on results from previous studies, showed that Echinacea increases the number of NK cells and that NK cells have a role in foetus rejection and in spontaneous abortions (De Fougerolles and Baines, 1987; Gendron and Baines, 1988). There is evidence from human studies suggesting that abnormalities in uterine NK cell numbers of function can lead to pregnancy complications such as recurrent miscarriage, preeclampsia or infertility (Mahajan et al., 2022). However, there are currently no studies linking the effects of Echinacea on NK and pregnancy complications.

168. 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 enzymes, in particular CYP3A4 (Modarai et al., 2010) and CYP2E1 (Raner et al., 2007). In addition, E. purpurea has demonstrated mild inhibitory activity towards P-glycoprotein in vitro (Hansen and Nilsen, 2009; Husain et al., 2023). Penzak et al. (2010) investigated the effects of E. purpurea 1,500 mg/day for 28 days on the pharmacokinetics of lopinavir-ritonavir using midazolam and fexofenadine as CYP3A4 and P-glycoprotein probes, respectively. They reported that the pharmacokinetics of lopinavir/ritonavir and fexofenadine were not influenced by Echinacea co-administration, whilst the clearance of midazolam increased, suggesting CYP3A4 induction. A study by Gorski (2004) confirmed the inhibitory effect of commercially available E. purpurea root extract preparation, taken at 1,600 mg daily for 8 days, on CYP2C9 and CYP1A2 in 12 healthy human volunteers. The authors only considered the effects on CYP1A2 as clinically significant with the potential to increase the toxicity of narrow therapeutic window drugs such as theophylline. However, there are no reports in the literature of an interaction between Echinacea and theophylline. The results from the same study indicate that Echinacea could also inhibit the intestinal CYP3A4 isoform, but not the hepatic form. Another human study (Gurley et al., 2004) using E. purpurea 1,600 mg/day for 28 days in 12 healthy volunteers reported no significant changes in the activities of CYP3A4, CYP2E1, and CYP2D6. There was a mild inhibition on CYP1A2, but it was not statistically significant. These results suggest that Echinacea may have the potential to interact with prescription medication during pregnancy, but the exact effects are unclear due limited clinical data on these interactions.

169. 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 are not considered to pose a health risk to the public (Filipiak-Szok et al., 2015; Raman et al., 2004).