# Conclusions and Questions

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## Conclusions

170. 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.

172. 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. Herbal products containing *E. purpurea*, *E. angustifolia* and *E. pallida* 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 4-10% of pregnant women use *Echinacea* for the treatment and prevention of cold/flu and immune system support.

173. 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.

174. 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.

175. The doses used in clinical studies on the efficacy of *Echinacea* are comparable to the estimated consumption of *Echinacea* of 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.

176. 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, immunosupression and diseases of the white blood cell system appears in the section.

177. 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* can affect the activity of CYP enzymes leading to inhibition of CYP1A2 and CYP3A4. One of the studies warned of potential toxicity if narrow therapeutic window drug substrates for CYP1A2, such as theophylline, are co-administered with *Echinacea*. This putative interaction has not been reported in the literature and its clinical relevance remains unclear.

178. 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.

# Questions for the committee

I. Is the Committee able to determine the risk to maternal health associated with *Echinacea* consumption?

II. Is it possible to derive a point of departure to be used in the risk assessment of *Echinacea*, based on the information presented in this discussion paper?

III. Does the Committee have any other comments on this paper?