Draft EFSA Scientific Opinion on the evaluation of the safety of preparations from the fruits of sweet and bitter fennel (Foeniculum vulgare Mill. and Foeniculum piperitum (Ucria) C.Presl)

Uncertainties (Section 4)

In this guide

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

58. Section 4 of the draft EFSA Opinion describes the uncertainties relating to: ADME of *p*-allylalkoxybenzenes, DNA adduct formation and repair, matrix effects and the exposure assessment (occurrence data, food consumption data and exposure scenarios). The key points have been summarised below, but please refer to the draft opinion for more detail.

ADME of *p*-allylalkoxybenzenes

59. The BMDL10 value used for risk assessment of *p*-allylalkoxybenzenes was derived for methyleugenol from a 2-year carcinogenicity study and EFSA applied this BMDL10 to the entire *p*-allylalkoxybenzene group because they possess similar structures, fates in the body and modes of action. This approach assumed the effects from combined exposure to single *p*-allylalkoxybenzenes to be additive with equal potency. The assumption was due to the absence of data on other *p*-allylalkoxybenzenes, preventing the identification of BMDLs10 for each single compound. Therefore, this method does not account for the likely possibility that each individual *p*-allylalkoxybenzene may have different carcinogenic potencies.

DNA adduct formation and repair

60. The estimation of DNA adduct formation in humans at background exposure levels (around 40-50 adducts per 10^8 nucleotides derived from methyleugenol) was based on studies on non-tumorous tissue samples from tumour patients or humanised mice (Herrmann et al., 2013; Herrmann et al., 2014). However, these findings may not be representative of tissues of healthy humans.

61. This section also describes uncertainties regarding the relationship between the amount of DNA adducts and tumorigenesis, the mechanism of formation of adducts and how they introduce mutations, interindividual variation in metabolism between humans and the risk of acute versus low level chronic exposure to *p*-allylalkoxybenzenes.

Matrix effects

62. There has been evidence that some compounds naturally present in herbs and spices were capable of inhibiting SULT enzymes and may therefore lead to the reduction of the formation of sulfooxy metabolites and DNA adducts

(Boberg et al., 1983; Alhusainy et al., 2013; Marabini et al., 2019). However, currently the findings have been limited by the use of a cell model incapable of replicating whole-body metabolism. Therefore, extrapolating these results to *in vivo* conditions was not possible.

Exposure assessment

63. Please see lines 1734-1799 of the draft EFSA opinion for the detailed discussion on uncertainties of the exposure assessment. Key points for each subsection are bulleted below.

Occurrence data

- EFSA used pooled values for the concentration of estragole in dried fennel fruits, fennel fruit infusions and infusions made from herbal blends containing fennel fruits for the exposure assessment.
- In several cases, the content in the food had to be estimated from concentrations of the *p*-allylalkoxybenzenes in the essential oil combined with the essential oil yield.
- Concentrations in some of the dried spices/herbs were estimated from concentrations in fresh spices/herbs or vice versa depending on the case.
- Non-EU food data were used in cases when EU data was absent. The non-EU food samples generally had higher levels of *p*-allylalkoxybenzenes than food sampled in EU countries, suggesting a potential under- or overestimation.
- Occurrence data of *p*-allylalkoxybenzenes for some commonly consumed foods were not available and were therefore not considered for the exposure assessment, leading to a possible underestimation of exposure.
- Exposure from food supplements was not included in the assessment and may lead to underestimation of the exposure to *p*-allylalkoxybenzenes.

Food consumption data

- Consumption of herbs and spices, such as dried fennel fruits, may have been underreported in the EFSA Comprehensive Food Consumption Database as they are often not accurately captured in surveys.
- Difficulties to accurately quantify amounts used/portions of fennel fruits and other herbs and spices may lead to under- or overestimation, based on the assumptions made. There is also uncertainty due to a wide variability in cultural and individual preferences.

- It was unknown how well the exposure assessment performed in capturing exposure from *p*-allylalkoxybenzene-containing flavourings and food ingredients that have been added to compound foods.

Exposure scenarios

- Unspecified herbal blends were assumed to contain fennel fruits within the fennel fruit infusion exposure scenario. This assumption was made to obtain more reliable, and conservative estimated of exposure to *p*-allylalkoxybenzenes. Estimates shown for the whole population have been produced without this assumption and hence were likely to underestimate the importance of the contribution of fennel fruits to total *p*-allylalkoxybenzene exposure.