ADME of other p-allylalkoxybenzenes (Section 3.4)

In this guide

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

20. The draft EFSA opinion did not discuss the ADME of other *p*-allylalkoxybenzenes. Only the metabolism of safrole and methyleugenol were briefly discussed (lines 792-802).

21. Safrole and methyleugenol are metabolised by the same pathways as estragole; however, PBBK models have demonstrated that the relative importance of each pathway differs (Al-Subeihi et al., 2012; Martati et al., 2012). *O*-demethylation of methyleugenol has been suggested to be less efficient than for estragole due to steric hindrance created by the two methoxy groups present in methyleugenol. The National Toxicology Programme (NTP) (2000) study found that only 0.1% of [^{14}C] could be recovered in breath of rats (as CO2 via *O*-demethylation). Metabolites of safrole were found to take much longer to be excreted than estragole and methyleugenol taking 120 hours instead of 24 hours, indicating safrole was metabolised slower than other *p*-allylalkoxybenzenes (Martati et al., 2012).

22. Please note the Al-Subeihi et al. (2012) reference is missing from the draft EFSA opinion but has been found and referenced within this summary document. This will be noted in the comments for EFSA.

23. EFSA also identified some evidence that *p*-allylalkoxybenzenes can cross the placenta, however, this was limited to a single study where DNA adducts were found in the foetus of pregnant ICR mice orally dosed with safrole at 97 mg/kg bw on day 18 of gestation (Lu et al., 1986).

24. EFSA also highlighted two studies that provided evidence of transfer of *p*-allylalkoxybenzenes into breast milk. Denzer et al. (2015) reported transfer of estragole from an ingested infusion into breast milk of lactating women, however, there was wide variation within the measured levels in breast milk ranging from 1 to 21 % of the ingested estragole dose. Vesselinovitch et al. (1979) demonstrated transfer of safrole into breast milk of B6C3F1 mice which was found to be cancerogenic in the male offspring. The lactating females were intragastrically exposed to 120 mg/kg bw safrole 12 times every second day after parturition.

25. The draft opinion also discusses tissue retention (section 3.3.1.4); however, no data was identified for estragole, only a single study with methyleugenol studying tissue distribution in Fischer 344 rats after a single oral dose of 118 mg/kg bw [^{14}C]methyleugenol (NTP, 2000). After 72 hours, 3.8 % of

the ingested labelled methyleugenol were still detectable in tissues with the highest concentrations found in the liver (mean 0.104 %), muscle (0.073 %), blood (0.068 %), skin (0.064 %) and fat (0.049 %). In other tissues the concentrations were 0.01 %.