In vitro metabolism of alternariol and alternariol monomethylether in rat liver microsomes

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Alternariol (AOH) and alternariol monomethylether (AME) are the major mycotoxins produced by molds of the genus *Alternaria*, in particular *A. alternata*, which occur ubiquitously on plants and other organic materials. AOH and AME have been found in many kinds of foodstuff, e.g. grains, sunflower seeds, oilseed rape and pecans as well as in various fruits including tomatoes, olives, mandarins, melons, peppers, apples and raspberries. The German Federal Institute of Risk Assessment (BfR) has recently pointed out that there is an urgent need for more information about the toxicity of alternaria toxins, because data published so far do not allow to assess the health risk for the consumer. In fact, only few data are available about the toxicity of AOH and AME. In particular, information about the biotransformation of AOH and AME is scarce and inconsistent.

Therefore, we have initiated studies on the phase I and phase II metabolism of AOH and AME in liver microsomes of male Sprague-Dawley rats. Incubations were carried out with microsomes fortified with NADPH for oxidative metabolism and with activated glucuronic acid (UDPGA) for conjugation. AOH and AME and their metabo-lites were extracted from the incubations and analyzed by HPLC. The metabolites were then characterized by their UV/VIS spectra and by GC MS.

AOH gave rise to four and AME to five hydroxylated metabolites, most of which were catechols. Furthermore, AME was demethylated to AOH. In addition, some products with a lower polarity and with similar UV/VIS spectra as the parent mycotoxins were detected. The addition of antioxidants (ascorbic acid or glutathione) decreased the formation of these products and increased the generation of the hydroxylated meta-bolites. This finding led to the conclusion that the less polar products are formed by further reaction, e.g. polymerisation, of the hydroxylated metabolites.

In microsomal incubations of AOH and AME with UDPGA, two glucuronides of each mycotoxin were observed. Whereas the two AOH glucuronides were formed in about equal amounts, the ratio of the two AME glucuronides was 7:1.

Our studies have shown that both AOH and AME undergo extensive metabolism *in vitro*. Whereas conjugation with glucuronic acid probably leads to detoxification of the mycotoxins, the observed oxidation to catechols may represent a pathway generating reactive metabolites. Further investigations are needed to clarify the toxicological relevance of the metabolism of the alternaria toxins.