STRUCTURE ACTIVITY RELATIONSHIPS FOR THE CHEMICAL BEHAVIOUR AND TOXICITY OF ELECTROPHILIC QUINONES / QUINONE METHIDES

Ivonne M.C.M. Rietjens\textsuperscript{1,2,3}, Hanem M. Awad\textsuperscript{1}, Marelle G. Boersma\textsuperscript{1}, Marlou L.P.S. van Ierse\textsuperscript{1)}, Jacques Vervoort\textsuperscript{1)} and Peter J. Van Bladeren\textsuperscript{2,3)}

1) Laboratory of Biochemistry, Wageningen University, Dreijenlaan 3, 6703 HA Wageningen, The Netherlands  
2) Division of Toxicology, Wageningen University, Tuinlaan 5, 6703 HE Wageningen, The Netherlands.  
3) TNO/WU Centre for Food Toxicology, PO Box 8000, 6700 EA Wageningen, The Netherlands

INTRODUCTION

Electrophilic quinones and quinone methides from a variety of natural and synthetic compounds have been classified as likely toxic reactive metabolites. This includes the quinones / quinone methides of catechol-type metabolites from estrogens and polycyclic aromatic hydrocarbons\textsuperscript{1,2,3}. Metabolic activation of estrogens to redox active and/or electrophilic metabolites has been proposed as one of the mechanisms responsible for the link between estrogen exposure and the risk of developing cancer\textsuperscript{1,2}. Especially catechol (ortho-diol)-type of metabolites resulting from cytochrome P450 catalysed hydroxylation of estrogens (Figure 1) may be involved.

\begin{equation}
\begin{array}{c}
17\beta\text{-estradiol} \\
\text{estrone} \\
equiulin \\
\text{equilenin}
\end{array}
\begin{array}{c}
\text{P450} \\
\text{P450} \\
\text{P450}
\end{array}
\begin{array}{c}
\text{estrone} \\
\text{2-OH-estrone} \\
\text{4-OH-estrone} \\
\text{4-OH-equilenin} \\
\text{4-OH-equilenin}
\end{array}
\end{equation}

\textbf{Figure 1.} Metabolism of endogenous and equine estrogens to catechol metabolites by cytochromes P450\textsuperscript{1,2}.
The involvement of catechol-type metabolites has also been outlined to play a role in the metabolic activation of polycyclic aromatic hydrocarbons\textsuperscript{3,3}. In addition to the conversion of the dihydrodiol metabolites to diol-epoxides by cytochromes P450, the conversion of the dihydrodiol metabolites of polycyclic aromatic hydrocarbons by dihydrodiol dehydrogenase may result in formation of reactive catechol-type metabolites (Figure 2). These catechol-type metabolites are suggested to contribute to the carcinogenicity and toxicity of the aromatic hydrocarbons.

![Figure 2. Metabolic activation of polycyclic hydrocarbons to catechol metabolites\textsuperscript{3,3}.]

Figure 2 presents the mechanism behind the redox chemistry and alkylating toxicity of catechol-type metabolites from estrogens and polycyclic aromatic hydrocarbons. Redox cycling between the catechol and its quinone generates reactive oxygen species able of damaging the DNA. In addition, oxidation of the catechols to quinones and their isomeric quinone methides (see below) generates potent electrophiles that could alkylate DNA.

![Figure 3. Schematic presentation of the redox chemistry and alkylating toxicity of catechol-type metabolites from estrogens and polycyclic aromatic hydrocarbons.]

Taking this toxic pro-oxidative behaviour of catechol metabolites into account it is of interest that many flavonoids already contain this catechol-type structural element without the need for metabolic activation. This especially holds for flavonoids like for example quercetin, luteolin, taxifolin and fisetin containing a 3',4'-dihydroxy structural element (Figure 4). For these 3',4'-dihydroxyflavonoids their pro-oxidative quinone / quinone methide chemistry is especially of interest because of their increasing use as functional food ingredients and/or food supplements.