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**Sanofi-Aventis Preis für den besten Kurzvortrag**

Metabolic Activation of the Antibacterial Triclocarban by Cytochrome P450 1A1  
Yielding Glutathione and Protein Adducts

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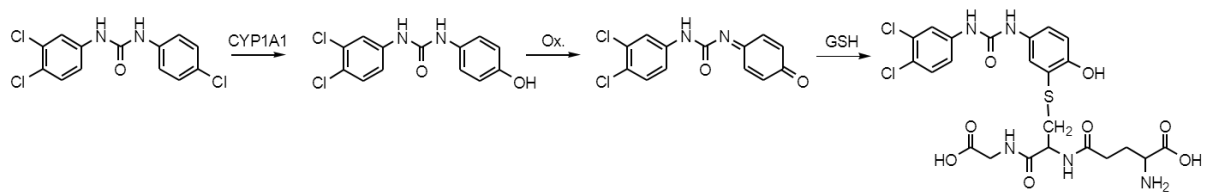
Triclocarban (TCC) is a common antimicrobial preservative in personal care products, particularly in bar soaps. TCC accumulates in the aquatic environment and has biological effects on mammals. For example, it is a potent inhibitor of the soluble epoxide hydrolase, an enzyme of the arachidonic cascade thus raising the possibility of detrimental effects upon human exposure. Bathing with TCC-containing soaps results in deposition of TCC on human skin and a small portion of this amount traverses the epidermal barrier. The absorbed TCC is extensively metabolized by Cytochrome P450 monooxygenases (CYPs). In order to investigate whether the metabolic activation of TCC might occur in skin incubations with spontaneously immortalized human epidermal keratinocytes (SIK), a minimally deviated epidermal culture model, were carried out with and without pre-induction with the Ah-receptor agonist TCDD. Upon treatment, TCC was rapidly absorbed from the medium (2  $\mu\text{M}$ ) reaching a level of  $2.04 \pm 0.27$  nmol/mg protein. At baseline a small but significant portion of the absorbed TCC was oxidatively metabolized by SIK while pre-incubation of SIK with 10 nM TCDD dramatically augmented metabolism of TCC. In order to test whether reactive metabolites were formed, proteins recovered from SIK incubations with  $^{14}\text{C}$ -TCC were isolated, and the levels of bound radioactivity were measured by accelerator mass spectrometry. Up to  $23 \pm 2$  pmol/mg TCC equivalents were covalently bound to cellular protein after 24 h of incubation in cells induced with TCDD [1]. Consistent with these findings, TCC-glutathione adduct peaks were detected in liquid chromatography (LC) analysis and scintillation counting following incubation of  $^{14}\text{C}$ -TCC with CYP1A1, the major TCDD-inducible CYP-isoform. The main GSH-adduct was thoroughly characterized by means of liquid chromatography with high resolution mass spectrometry [2]. These results suggest that TCC is activated via oxidative dehalogenation yielding a reactive para quinone imine (Fig.1). Overall, the reactive metabolites were only found in low levels which does not necessarily translate to potential adverse health effects following the use of TCC in personal care products. However, it is a surprise that reactive metabolite formation of

this major ingredient in personal care products has been overlooked for more than 50 years of usage.

**Literatur:**

[1] N.H. Schebb, B. Buchholz, B.D. Hammock and R.H. Rice (2012) Metabolism of the Antibacterial Triclocarban by Human Epidermal Keratinocytes to Yield Protein Adducts. *J Biochem Mol Toxic*, 26 (6), 230-234.

[2] N. H. Schebb, J. B. Muvvala, D. Morin, A. R. Buckpitt, B. D. Hammock and R. H. Rice (2014) Metabolic activation of the antibacterial agent, triclocarban, by cytochrome P450 1A1 yielding glutathione adducts. . *Drug Metab Dispos*, doi:10.1124/dmd.114.058206



**Fig.1** Suggested route for metabolic activation of the antibacterial triclocarban (TCC)