Dermatotoxicological and other Safety Testing Methods without Animals - State November 2013

Session 1: Dermatotoxicological risk assessment without animal testing

Skin metabolism in in vitro methods: Impact on skin sensitization and genotoxicity testing using aromatic amine hair dyes as an example of xenobiotics

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Skin is the first site of contact for aromatic amine hair dyes and characterisation of their skin metabolism is relevant to understand local and systemic effects occurring following skin exposure. We have compared the metabolism of key aromatic amine structures used in oxidative hair dyes in human keratinocytes (cell line HaCaT) with that observed in living human skin ex-vivo. N-acetylated derivatives were the major metabolites detected following exposure of HaCaT cells and living human skin, respectively, indicating that N-acetylation was the predominant phase II pathway. In the rat model, topical application was generally associated with a relatively high degree of N-acetylation compared to oral administration where sulfation and glucuronidation were more important. Results from human studies with realistic exposure to hair dye products containing p-phenylenediamine (PPD) and m-aminophenol indicate that N-acetylation of the hair dye precursors as well as the reaction products occurred under realistic use conditions. The predominant role of the enzyme N-acetyltransferase 1 (NAT-1) in aromatic amine skin metabolism is in line with the findings that the majority of the different aromatic amine structures used in oxidative hair dyes exhibit substantial N-acetylation rates when incubated with the recombinant human enzyme. On the other hand, activation of oxidative metabolism was not found in living human skin and could only occur when HaCaT cells were exposed to very high concentrations of PPD. In conclusion, NAT-1 dependent dermal N-acetylation of mononuclear aromatic amine hair dyes is considered to represent a relevant 'first-pass' metabolism effect in the skin by reducing the amount of the parent aromatic amine prior entering the systemic circulation. For the endpoints skin sensitization and genotoxicity in vitro data in vivo data indicate that N-acetylation represents a "first pass" detoxification effect in the skin considered relevant for risk assessment following topical exposure.