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Meeting abstract

Impact of stereochemistry on biological effects of permethrin: induction of apoptosis in human hepatoma cells (HCC-1.2) and primary rat hepatocyte cultures

Julia Dornetshuber[1], Wolfgang Bicker[2], Michael Lämmerhofer[2], Wolfgang Lindner[2], Anneliese Karwan[1] and Wilfried Bursch*[1]

Address: [1]Department of Medicine I, Institute of Cancer Research, Research Unit Toxicology and Prevention, Medical University of Vienna, Austria and [2]Institute of Analytical Chemistry and Food Chemistry, University of Vienna, Austria

Email: Wilfried Bursch* - wilfried.bursch@meduniwien.ac.at

* Corresponding author

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Stereochemistry plays a crucial role in determining the toxicological profile of many chiral xenobiotics, e.g. the insecticidal action of mixtures containing the four stereoisomers of permethrin is essentially brought about by the (1*R*, *cis*)- and (1*R*, *trans*)-forms. Primarily non-ion channel related mammalian effects like induction of cytochrome P450 enzymes and inhibition of mitochondrial complex I – relevant endpoints in elucidating a chemical's mode of action and thus toxicological risk assessment – were elucidated in studies with four-isomer mixtures of permethrin only [1-3]. Therefore, we initiated a project to shed light on the stereoselectivity of permethrin effects in mammals, using human hepatoma cells (HCC-1.2) and primary rat hepatocyte cultures as test models. Here we report (1) a commercially available four-isomer mixture of permethrin (*cis*-racemate/*trans*-racemate ~ 25:75) exhibited a dose-dependent (2–50 μM) pro-apoptotic activity; (2) the physiological death signal TGF-β1 (10 ng/ml) and permethrin exerted an additive pro-apoptotic effect; (3) purified permethrin stereoisomers, i.e. (1*R*, *cis*), (1*S*, *cis*), (1*R*, *trans*), (1*S*, *trans*), exhibited – in contrast to their insecticidal action – no significant differences in their pro-apoptotic action as compared to the four-isomer mixture; (4) the pro-apoptotic potency of permethrin was lost upon metabolism to permethrinic acid, 3-phenoxybenzyl alcohol, and 3-phenoxybenzoic acid.

References

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