Comparison of efficacy, toxicity, and analytical impurity content of reference and generic versions of transfluthrin

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Requirements on bioequivalence and relevant impurities are in place for the evaluation and registration of new compounds with biocidal or pesticidal activities. However, the registration requirements for established compounds from new suppliers or for established compounds produced by a different manufacturing process have been less clear and ambiguity exists as to how ‘equivalence of health hazards’ can unequivocally be demonstrated analytically and by toxicological assays. The case presented in this analysis focuses on the chiral pyrethroid transfluthrin (TFL) and chemically reactive impurities in low concentrations (<0.1 %) difficult to capture analytically. This study compares reference TFL with commercialized generic TFLs from two alternative manufacturing sources in India and China. Despite their apparent high racemic purity these TFLs were biologically less effective, genotoxic in the Ames’ assay, demonstrated sensory lung irritation and lung/skin sensitization in specialized bioassays. Additionally, these TFLs demonstrated a high batch-to-batch variability. In contrast, the off-patent reference TFL was unequivocally negative in all assays. Tier I analytical assays failed to detect the most relevant, critical impurity in the absence of impurity-specific optimized analytical procedures. These findings suggest that a well-balanced, combined approach of analytical and toxicological assays provides the best means to assure objectively that all impurities deemed to be critical are identified and accounted for. In summary, this study demonstrates that ‘structural alert’-based toxicity tests proved to be more predictive than any indiscriminant battery of standard bioassays commonly applied to demonstrate equivalence. This applies specifically to chemically reactive impurities that may undergo site reactions during their analytical work-up.