In vivo comparison of the proangiogenic properties of chlordecone and three of its dechlorinated derivatives formed by in situ chemical reduction

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Résumé en anglais	In situ chemical reduction (ISCR) has been identified as a possible way for the remediation of soils contaminated by chlordecone (CLD). Evidences provided by the literature indicate an association between the development of prostate cancer and CLD exposure (Multigner et al. 2010). In a previous in vitro study, we demonstrated that the two main dechlorinated CLD derivatives formed by ISCR, CLD-1Cl, and CLD-3Cl have lower cytotoxicity and proangiogenic properties than CLD itself (Legeay et al. 2017). By contrast, nothing is known on the in vivo proangiogenic effect of these dechlorinated derivatives. Based on in vitro data, the aims of this study were therefore to evaluate the in vivo influence of CLD and three of its dechlorinated metabolites in the control of neovascularization in a mice model of prostate cancer. The proangiogenic effect of CLD and three of its dechlorinated derivatives, CLD-1Cl, CLD-3Cl, and CLD-4Cl, was evaluated on a murine model of human prostate tumor (PC-3) treated, at two exposure levels: 33 µg/kg and 1.7 µg/kg respectively reflecting acute and chronic toxic exposure in human. The results of serum measurements show that, for the same ingested dose, the three metabolite concentrations were significantly lower than that of CLD. Dechlorination of CLD lead therefore to molecules that are biologically absorbed or metabolized, or both, faster than the parent molecule. Prostate tumor growth was lower in the groups treated by the three metabolites compared to the one treated by CLD. The vascularization measured on the tumor sections was inversely proportional to the rate of dechlorination, the treatment with CLD-4Cl showing no difference with control animals treated with only the vehicle oil used for all substances tested. We can therefore conclude that the proangiogenic effect of CLD is significantly decreased following the ISCR-resulting dechlorination. Further investigations are needed to elucidate the molecular mechanisms by which dechlorination of CLD reduces proangiogenic effects in prostate tumor.
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