

Prediction of in vivo genotoxicity of lasiocarpine and riddelliine in rat liver using a combined in vitro-physiologically based kinetic modelling-facilitated reverse dosimetry approach

Lu Chen^{*1}, Ad Peijnenburg², Laura de Haan¹, Ivonne M.C.M. Rietjens¹

¹) Division of Toxicology, Wageningen University, PO Box 8000, 6700 EA Wageningen, The Netherlands

²) Wageningen Food Safety Research, PO Box 230, 6700 AE, Wageningen, The Netherlands

*Corresponding author:

Lu Chen

Division of Toxicology, Wageningen University,

Stippeneng 4, 6708 WE Wageningen,

The Netherlands

Fax: +31 317 484 931

Phone: +31 317 483 971

E-mail: Lu.Chen@wur.nl

Supplementary Material

Table 1 In vitro genotoxicity data of lasiocarpine and riddelliine derived from primary rat hepatocytes, and dose reconstructed based on AUC and C_{max} using PBK model

Compound	Compound concentration (μM)	Cell number (%)	γH2AX induction	The effect concentration in rat serum (μM) ^a	Concentrations based on AUC	Dose reconstructed based on AUC using PBK model (mg/kg bw)	Dose reconstructed based on C _{max} using PBK model (mg/kg bw)
Lasiocarpine	0, 0.006, 0.012, 0.024, 0.048 ^{**} , 0.09 ^{**} , 0.195 ^{**} , 0.39 ^{**} , 0.78 ^{**} , 1.56 ^{**} , 3.125 ^{**} , 6.25 ^{**}	116, 101, 102, 104, 104, 109, 103, 103, 108, 111, 110, 109	1.00, 1.01, 1.08, 1.10, 1.15, 1.21, 1.26, 1.31, 1.33, 1.37, 1.40, 1.45	0, 0.009, 0.019, 0.038, 0.075, 0.14, 0.31, 0.61, 1.22, 2.44, 4.88, 9.77	0, 0.225, 0.45, 0.9, 1.8, 3.38, 7.31, 14.63, 29.25, 58.5, 117.19, 234.38	0, 2.80, 5.19, 10.28, 18.66, 31.23, 55.47, 85.40, 120.12, 157.83, 200.03, 250.92	0, 0.43, 0.50, 0.65, 0.94, 1.30, 2.80, 5.19, 9.68, 17.46, 30.03, 48.89
Riddelliine	0, 0.065, 0.13 ^{**} , 0.26 ^{**} , 0.52 ^{**} , 1.04 ^{**} , 2.08 ^{**} , 4.16 ^{**} , 8.32 ^{**} , 10 ^{**} , 15 ^{**}	116, 106, 111, 107, 104, 102, 110, 108, 102, 96, 96	1.00, 1.11, 1.13, 1.15, 1.17, 1.25, 1.33, 1.36, 1.39, 1.49, 1.62	0, 0.098, 0.20, 0.39, 0.79, 1.58, 3.15, 6.30, 12.61, 15.15, 22.72	0, 2.36, 4.72, 9.45, 18.91, 37.82, 75.64, 151.27, 302.55, 363.64, 545.45	0, 1.60, 3.24, 6.37, 12.33, 22.92, 40.67, 67.07, 101.38, 111.67, 136.58	0, 0.41, 0.55, 0.82, 1.20, 2.37, 4.68, 9.14, 17.28, 20.37, 28.86

^a The effect concentration of lasiocarpine (LC) or riddelliine (RD) in rat serum (C_{LC/RD, rat serum}) was corrected by the following equation: $C_{LC/RD, rat serum} = C_{ub, in vitro} / f_{ub, rat}$ serum. Where C_{ub, in vitro} is the unbound concentration of lasiocarpine or riddelliine in the in vitro culture medium. The f_{ub} for lasiocarpine and riddelliine were 0.64 and 0.66, respectively.

^{**} Significantly different from the control group (P≤0.05) by *t*-test.