# Physiologically based kinetic modeling of the bioactivation of myristicin

**Amer J. Al-Malahmeh1,2 · Abdelmajeed Al-Ajlouni1,2 · Sebastiaan Wesseling1 · Ans E. M. F. Soffers1 · Ala'Al-Subeihi4 · Reiko Kiwamoto1 · Jacques Vervoort3 · Ivonne M. C. M. Rietjens1**

The present study describes physiologically based kinetic (PBK) models for the alkenylbenzene myristicin that were developed by extension of the PBK models for the structurally related alkenylbenzene safrole in rat and human. The newly developed myristicin models revealed that the formation of the proximate carcinogenic metabolite 1′-hydroxymyristicin in liver is at most 1.8 fold higher in rat than in human and limited for the ultimate carcinogenic metabolite 1′-sulfoxymyristicin to (2.8–4.0)-fold higher in human. In addition, a comparison was made between the relative importance of bioactivation for myristicin and safrole. Model predictions indicate that for these related compounds, the formation of the 1′-sulfoxy metabolites in rat and human liver is comparable with a difference of results in MOE values for myristicin that amount to 1000– 2700, indicating a priority for risk management. The results obtained illustrate that PBK modeling provides insight into possible species differences in the metabolic activation of myristicin. Moreover, they provide an example of how PBK modeling can facilitate a read-across in risk assessment from a compound for which in vivo toxicity studies are available to a related compound for which tumor data are not reported, thus contributing to alternatives in animal testing.

Amer J. Al-Malahmeh1,2 · Abdelmajeed Al-Ajlouni1,2 · Sebastiaan Wesseling1 · Ans E. M. F. Soffers1 · Ala'Al-Subeihi4 · Reiko Kiwamoto1 · Jacques Vervoort3 · Ivonne M. C. M. Rietjens1,2017, Physiologically based kinetic modeling of the bioactivation of myristicin, Archives of toxicology.