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Cancer risk assessment for dioxane based upon a physiologically-based pharmacokinetic approach

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SUMMARY

A cancer bioassay conducted in 1974 (Kociba et al.) indicated that rats given drinking water containing dioxane at a dose of $1184 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ produced an increased incidence of liver tumors. Applying the linearized multistage extrapolation model to these data, the administered dose estimated to present a human cancer risk of 1 in 100 000 (10^{-5}) was $0.01 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. As in customary regulatory policy, this estimate assumed that humans were about 5.5 times more sensitive than rats on a mg/kg basis. However, this approach did not consider that the metabolism of dioxane is saturable at high doses. Based on experience with similar chemicals, it is known that the conventional risk extrapolation method may overestimate the most likely human cancer risk. In order to determine more accurately the likely human response following lifetime exposure to dioxane, a physiologically-based pharmacokinetic (PB-PK) model was developed. The objective of this study was to establish a quantitative relationship between the administered dose of dioxane and the internal dose delivered to the target organ. Using this PB-PK model, and assuming that the best dose surrogate for estimating the liver tumor response was the time-weighted average lifetime liver dioxane concentration, the cancer risk for humans exposed to low doses of dioxane was estimated. The dose surrogate in humans most likely to be associated with a tumorigenic response of 1 in 100 000 is $280 \mu\text{mol/l}$, equivalent to an administered dose of about $59 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. The 95% lower confidence limit on the dose surrogate at the same response level is $1.28 \mu\text{mol/l}$, equivalent to an administered dose of $0.8 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. This PB-PK analysis indicated that conventional approaches based on the administered doses in the rodent bioassay, if uncorrected for metabolic and physiological differences between rats and humans, will overestimate the human cancer risk of dioxane by as much as 80-fold.