

Project No. 87-H6 - Tree and Crop Research
Methyl Bromide Studies

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Objectives: Based on pharmacokinetic modeling, evaluate the carcinogenic risk resulting from dietary exposure to methyl bromide.

Progress and Plans - The EPA is moving toward requiring a carcinogenesis bioassay of methyl bromide administered by the oral route. Since with proven technology it is impossible to prepare a stable admixture of methyl bromide with the animal feed, it would be necessary to administer the compound via gavage, (i.e., directly into the stomach via a tube). These are the conditions under which hyperplasia, and perhaps carcinogenesis of the rat forestomach have been observed in Dutch and U.S. studies. Gavage administration of an irritant such as methyl bromide is not necessarily a valid surrogate for a feeding study when local lesions are observed. If a gavage study were to be attempted, it would require dilution of the methyl bromide with a bulk nutrient mixture. This would create a technically difficult situation with respect to administration through a tube.

It is highly likely that a two-year study of methyl bromide administered by gavage at concentrations associated with local irritation will result in the formation of forestomach tumors in rats and such a response will provide very little of the needed information for evaluating the health effects of dietary methyl bromide.

For these reasons, efforts to develop a pharmacokinetic model evaluating the carcinogenic risk resulting from dietary exposure to methyl bromide were initiated. Current efforts are focusing on gastrointestinal absorption and

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the resulting liver concentrations of ingested methyl bromide and how these relate to exposure by inhalation by test rats. Absorption from the gastrointestinal tract results in transitory higher liver concentrations than would occur because of inhalation. A key question is: would extrapolation from inhalation studies sufficiently account for potential liver carcinogenicity? This depends on the nature and extent of a number of metabolic and kinetic factors. Work is proceeding on submodels to help answer this question either by using existing data or by identifying experiments necessary to obtain the required data.

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