IDENTIFICATION OF THE MODE OF ACTION OF CARCINOGENS

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An important objective in toxicological studies is the detection of carcinogenic hazards of agents in the environment or used by humans. Since classical toxicological studies and especially longterm carcinogenicity bioassays are cost- and time-intensive, surrogate biomarkers of effect are investigated. As the liver is a target organ for a large proportion of carcinogenic agents, and foci of altered liver cells have been identified as precursors of carcinoma, these lesions have been used as endpoints in small size toxicological studies. It has been suggested that initiation increases the number of foci without changing their size distribution and that the size of existing foci increases without changing their number during promotion. It has also been assumed that an agent may possess both initiating and promoting activities. A question of high interest is whether the initiating or the promoting potential is the predominant mode of action. Using different data sets from chemical and from radiation carcinogenesis, we found that to discern between initiating and promoting potential, model-based analyses may be the only successful means. Several stochastic hepatocarcinogenesis models have been developed to describe the process of formation and growth of foci. They will be applied to data using maximum likelihood methods. Conclusions concerning the mode of action of the different agents basically remain unchanged for different models.