INTRODUCTION

Aflatoxin $B_1$ (AFB$_1$) is the most toxic and carcinogenic member of a family of difuranocoumarins produced as secondary metabolites by strains of Aspergillus flavus and related fungi$^1$. Exposure to aflatoxin is a public health hazard in technologically developing areas of the world, where AFB$_1$-producing fungi are distributed widely and where food production and storage conditions are conducive to mold spoilage and consequent mycotoxin production. In most animals, the main target for the biological effects of AFB$_1$ is the liver, although the relative sensitivity of different animal species varies markedly; the rat, rainbow trout and duck are highly sensitive whereas the mouse is resistant. The liver is also apparently a target in humans, in that a high incidence of hepatocellular carcinoma has been observed in chronically exposed populations$^2$. Additional factors may act in concert in initiating the putative carcinogenic effects of AFB$_1$ in humans; these include abnormal nutritional status or concomitant pathological conditions such as viral hepatitis.
In recent years we have been examining the metabolism and macromolecular-binding characteristics of AFB\textsubscript{1} with the objective of determining how these factors relate to its biological effects in animals and humans. We have emphasized studying the interactions of metabolically activated forms of carcinogens with DNA, an approach engendered by the key role of this macromolecule as the cellular repository of genetic information. Thus, it represents an inherently reasonable site at which chemical damage by carcinogen-DNA adduct formation can be fixed biologically. In a mechanistic sense, the presence of adducts could lead to temporary alteration in the regulation of gene function, or it could abnormally affect the fidelity of transcription or replication. Alternatively, structural modification of DNA by covalent adduct formation might cause gene rearrangement or result in the induction of an error-prone repair process and thus indirectly cause fixation of the molecular lesion. It is our working hypothesis that aflatoxin adducts somehow alter the functional properties of DNA, most likely by mechanisms initiated by somatic cell mutation. Ultimately, these initiating events may result in transformation of normal cells into cancer cells, albeit by processes that are not well understood at present.

This review summarizes the current status of our efforts toward developing an understanding of the molecular mechanisms underlying the biological effects of AFB\textsubscript{1}. We will describe the biochemical pathways through which aflatoxin is activated and becomes bound to DNA, with the specific objective of relating the qualitative, quantitative and kinetic features of binding to initiating events in carcinogenesis.

PATHWAYS OF METABOLIC ACTIVATION OF AFLATOXIN B\textsubscript{1} AND FORMATION OF DNA ADDUCTS

Metabolism is required to convert AFB\textsubscript{1} to chemically reactive, DNA-binding forms that presumably are responsible for its potent biological effects. (Known transformations of AFB\textsubscript{1} are summarized in Fig. 1.) The predominant AFB\textsubscript{1} metabolite that binds to DNA in animal and human tissues is the AFB\textsubscript{1}-2,3-oxide\textsuperscript{3-8}. The stereochemistry of this epoxide was determined through in vitro studies\textsuperscript{5}, and it is evident that the mixed function oxidase activity that biotransforms AFB\textsubscript{1} stereoselectively produces the \(\beta\) or exo isomer. The epoxide possesses such a high degree of reactivity that it has never been isolated, despite numerous attempts to do so in this laboratory and others. Its structure was established mainly on the basis of indirect evidence, including identification of the AFB\textsubscript{1}-2,3-dihydrodiol as an acid degradation product of AFB\textsubscript{1}-modified RNA and DNA\textsuperscript{3,4}, and identification of the absolute structure of the primary adduct that the epoxide forms upon interaction with guanyl residues in DNA\textsuperscript{5,6}. 