SECTION I

METABOLISM AND KINETICS OF TOXIC CHEMICALS
I. FUNDAMENTAL CONCEPTS

by
D.V. Parke

In the safety evaluation of chemicals, the basic reasons for undertaking metabolism and toxicokinetic studies are to elucidate the mechanisms of toxicity of the chemicals in question and to facilitate the extrapolation of experimental animal toxicity data to humans. Chemical toxicity arises from reactions between the ingested toxic chemical, or one or more of its metabolites with chemical constituents of the body. For example, an ingested chemical A may be metabolized into a "reactive intermediate" B, which can then undergo further metabolism by interaction with a body constituent, such as glutathione, to give metabolite C, which is then excreted in the urine or bile. Alternatively, "reactive intermediate" B may undergo further metabolism to a "proximate carcinogen" D, which may alkylate DNA, resulting in mutations and possibly carcinogenesis. The toxicity of the chemical will depend on the concentration of the "reactive intermediate" in the target tissue which in turn will depend on the rates of the alternative reactions B⟶C, and B⟶D. Reaction B⟶C would generally be a "detoxication" reaction, whereas the reaction B⟶D is a "metabolic activation".

A knowledge of the changes which the ingested chemical may undergo in the body enables us to understand the molecular mechanisms of toxicity. For example, the formation of the reactive intermediate epoxides of the polycyclic hydrocarbons leads to their interaction with glutathione (detoxication) or with DNA (activation) or results in their further metabolism to the less reactive phenols (detoxication). A knowledge of metabolism has also recently been shown to provide information on the likely integrity of the body's defence mechanisms against chemicals. Generally, these mechanisms act to protect the animal organism against the toxic effects of chemicals by detoxicating them and to protect against the toxicity of excess tissue oxygen (1,2). Interference with these enzymic detoxication mechanisms by highly toxic chemicals may result in toxicity not only from the toxic chemicals *per se* but also from autoxidative mechanisms resulting from damage of the body's chemical defence system. For