Many chemical carcinogens, including the polycyclic hydrocarbons, require metabolic activation before they can react with cellular macromolecules and probably before they can exert their biological effects (1). With the polycyclic hydrocarbons, this activation is carried out by both human and animal tissues, and the intermediates thus formed are believed to be epoxides (2). In this chapter, the overall metabolic pathways by which different types of epoxides are formed from polycyclic hydrocarbons, the routes by which these epoxides are further metabolized, and the structures of the epoxides that react with glutathione and probably with DNA in cells are considered.

FORMATION OF EPOXIDES IN THE METABOLISM OF POLYCYCLIC HYDROCARBONS

Simple Epoxides

Studies on the metabolism of polycyclic hydrocarbons have been carried out in a variety of systems including whole animals (3), cells in culture (4, 5), tissues in short-term organ culture (6), and tissue preparations obtained from both human and animal sources (7–9). Although there are some variations between the products obtained in the different types of experiments, the overall pattern of metabolites is very similar and, because of this, a great deal of the published work on hydrocarbon metabolism has been carried out using readily available...
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tissues such as rat liver, even though the hydrocarbons are usually considered to be biologically inactive in these tissues.

The initial process in the metabolism of the hydrocarbons is carried out by the monoxygenases present on the endoplasmic reticulum of cells, and the enzymes require NADPH and molecular oxygen. The primary products are simple epoxides which can be formed on either K-region or non-K-region bonds. The formation of K-region epoxides from a number of polycyclic hydrocarbons by microsomal fractions of rat liver (9) and lung (8) and of human lung (7) has been demonstrated directly, but with the exception of naphthalene, which is metabolized to naphthalene 1,2-oxide by rat liver microsomal fractions (10), direct evidence for the formation of simple non-K-region epoxides has not been obtained. However, since aromatic hydrocarbons are metabolized by tissue preparations to non-K-region dihydrodiols, it is presumed that these arise through the intermediate formation of non-K-region epoxides. Some tissues that probably metabolize polycyclic hydrocarbons to epoxides are listed in Table 1.

The simple epoxides are metabolized by one of the three metabolic routes shown in Fig. 1. The first route involves conjugation with glutathione and this is carried out by glutathione S-epoxide transferases that are present in the cytosol of cells of many tissues including liver and lung (11). K-region epoxides are much better substrates than non-K-region epoxides for these enzymes (12), and glutathione conjugates formed from non-K-region epoxides are not detected as metabolites when hydrocarbons such as benz[a]anthracene are metabolized by rat liver preparations. The glutathione conjugates are usually considered to be detoxication products since they are water soluble and are unlikely to reenter the microsomal lipid membrane. Moreover, there is no evidence to suggest that they are further metabolized to active species by microsomal enzymes, although in whole animals the simpler hydrocarbons are excreted as mercapturic acids that probably arise by the metabolism of glutathione conjugates at the peptide side chains (13).

The simple epoxides, both K-region and non-K-region, are also metabolized by a route that involves the hydration of these compounds with the formation of dihydrodiols, usually of trans configuration. The metabolism is carried out by epoxide hydrases (or hydratases) present on the endoplasmic reticulum of cells of many tissues (14). The dihydrodiols were once thought to be true detoxica-

1 Numbering system for benz[a]anthracene:

![Numbering System Diagram]