TYPES AND AMOUNTS OF CARCINOGENS AS POTENTIAL HUMAN CANCER HAZARDS

JOHN H. WEISBURGER AND GARY M. WILLIAMS

American Health Foundation
1 Dana Road
Valhalla, New York 10595-1599

Current knowledge on the mechanisms of chemical carcinogenesis forms the basis for application of select short-term in vitro and in vivo tests to detect potential human carcinogens, for ultimate application to hazard assessment. Chemical carcinogenesis involves a series of distinct steps, proceeding from the initiation of a neoplastic cell, through its promotion, development, and progression to cancer. Some chemicals act in each of these stages as initiators, cocarcinogens, promoters, or inhibitors of carcinogenesis. Chemicals can be classified as operating by genotoxic or epigenetic mechanisms, and appropriate tests can be used to detect such properties. These abbreviated tests provide enhanced qualitative decision-making potential since they are based on mechanisms of action. Advances in molecular biology may provide additional tests to detect cancer risk. The quantitative data available from in vitro dose-response studies indicate that carcinogenic effects are dose dependent and, therefore, a threshold or no-effect level probably exists, which is low for potent carcinogens (especially genotoxins) and high for weaker ones (particularly epigenetic agents).

INTRODUCTION

Substantial progress has been made in the complex field of cancer causation and development, especially as regards the understanding of the mechanisms of carcinogenesis. It is now possible to apply this knowledge to a more precise definition of chemicals as human cancer hazards, with emphasis on the qualitative and quantitative aspects.

2. Address correspondence to: J. H. Weisburger, American Health Foundation, 1 Dana Road, Valhalla, N.Y. 10595–1599; telephone (914) 592–2600.
MECHANISMS OF CARCINOGENESIS

Chemical carcinogenesis involves a series of defined steps that require, as a rule, a lengthy expression time from the beginning of exposure of cells and tissues until development of a cancer. In a first event, many chemical carcinogens are converted to an active form through biotransformation, although a few synthetic chemicals are directly reactive (Kocsis, 1986). The important metabolic activation reaction is subject to controlling elements derived from both the host (genetics) and environmental conditions (Fig. 1). The resulting product, a reactive chemical electrophile or radical cation, typically interacts with cellular macromolecules at nucleophilic centers (Miller and Miller, 1986). A key reaction occurs with DNA that, upon cell duplication, yields further gene alterations, including gene rearrangement and abnormal gene expression, particularly of the oncogene-containing codons. Thus, a cell with an abnormal genome is produced. This part of the process constitutes the genotoxic sequence (Williams and Weisburger, 1986), which is subject to enhancement by cocarcinogenic agents (Williams, 1984).

An “initiated” neoplastic cell can remain latent; i.e., it persists and replicates in a controlled manner so that it does not manifest itself. Tumor formation as a result of growth and development of the neoplastic cell requires the participation of host factors and also of external agents operating on growth control elements that may play a role in function and differentiation (Berenblum, 1985). Endogenous and, especially, exogenous promoters enhance this stage of the overall process, which may involve modification of membranes and receptors to release cells from growth control through as yet poorly known, epigenetic mechanisms, such as effects on intercellular communication, differentiation, and endocrine systems (Trosko et al., 1985; Williams, 1985).

Progression achieves the conversion of a benign tumor to a malignant, invasive cancer, or of a highly differentiated neoplasm to an anaplastic, undifferentiated cancer through ill-defined mechanisms, but probably involving introduction of additional alterations in the genetic apparatus (Shubik, 1984).

In contemporary terms, evaluation of human cancer hazards includes the capability to detect and quantitate genotoxic chemicals and other agents that act as promoters or enhancers. If progression is susceptible to external influences, procedures will be needed to detect chemicals affecting that part of the process (Weisburger and Williams, 1984).

Based on these principles, it is now possible to develop systematic in vitro and in vivo approaches to detect and classify chemicals as operating by genotoxic or by epigenetic mechanisms; i.e., whether they play a role in the carcinogenic process by modifying DNA and the genetic apparatus, or by other, usually enhancing, actions. We will briefly review the approaches to carcinogen bioassay we initially delineated ten years ago as the “Decision Point Approach” (Weisburger and