N-SUBSTITUTED AROMATIC COMPOUNDS

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INTRODUCTION

Aromatic compounds that have nitrogen atoms attached to their ring carbons have a potential for eliciting a variety of adverse cytotoxic, mutagenic and carcinogenic responses. The actual biological effects produced by these agents are dependent on their structure, the ability of the host organism to metabolize the compound and the response of the organism to the metabolites that are generated. Although this group of compounds is most often referred to as aromatic amines, the term N-substituted aromatic compounds is more appropriate since it is sufficiently broad to include both nitrocompounds that may be converted metabolically to aromatic amines, as well as metabolites of amines, e.g. hydroxamates, amides and nitroso derivatives, that have quite different chemical properties. This report is intended to provide insight into the carcinogenic potential of these compounds and the mechanisms by which they are believed to effect this activity.

The reader is directed to earlier reviews for additional details and alternative perspectives on the epidemiology (Parkes, 1976), structure activity relationships (Clayson and Garner, 1976) and mechanisms of action (Miller, 1978; and Irving, 1979) of aromatic amines.

HISTORICAL PERSPECTIVE

With the advent of synthetic organic chemistry in the 19th century, the production of synthetic dyes led to the recognition that bladder tumors were occurring in men engaged
in this industry years after their first exposure. Although these tumors were called "aniline cancers", evidence concerning the identity of the compounds responsible for these tumors came only in the 1930s when Hueper demonstrated that the administration of 2-naphthylamine to dogs resulted in the development of bladder cancer. Earlier the induction of liver tumors in rats by o-aminonitrotoluene had given the first indication of carcinogenic potential by a compound other than a polycyclic aromatic hydrocarbon. Since that time the greater understanding of the requirements for demonstration of carcinogenicity in experimental animals, increased efforts in this area and more detailed records concerning human exposure have led to the identification of a wide variety of N-substituted aromatic compounds that can induce cancer in man and animals. The structures, names and potential sources of exposure of carcinogens representative of this class are shown in Figure 1. Each have been shown to induce tumors in humans and/or experimental animals, save for the potent mutagen, 1-nitropyrene (Wang et al., 1980), which is only now being studied for determination of carcinogenic potential. Evidence of carcinogenicity in man has been obtained for 4-aminobiphenyl, benzidine, 2-naphthylamine, chlornaphazin and phenacetin, all of which can induce urinary bladder cancer (Parkes, 1976; Clayson & Garner, 1976). Phenacetin causes tumors of the renal pelvis as well (Bengtsson et al., 1978).

The criteria used to assess the carcinogenicity of these agents are those commonly applied in experimental carcinogenesis studies, i.e. an increase in the percentage of tumor-bearing animals, a decrease in the latent period for the development of tumors, and an increase in the number of tumors per animal. For example, a recent study of men engaged in benzidine production disclosed that 13 of 25 developed bladder tumors 15 to 20 years after their first exposure (Zavon et al., 1973). Their average age at the time of diagnosis was 47, approximately 20 years younger than the usual age at which men develop this disease. The frequent recurrences of bladder tumors can be regarded as an increased number of tumors per animal. In general, those compounds known to be carcinogenic in humans have induced tumors in experimental animals when adequately tested. To use the case of benzidine again, rats treated with a total dose as low as 8 mg developed both mammary and Zymbal gland tumors (Morton et al., 1981).

Prior to the late 1970s, it was believed that the structural requirements for an aromatic amine to be a carcinogen were that it contain at least 2 rings and that the position para to the nitrogen be occupied, or blocked, by an atom other than hydrogen. As the results of the massive National Cancer Institute tests for carcinogenicity have