



Chemical Carcinogenesis

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Understanding the relationship of chemicals to carcinogenesis has progressed significantly since the initial observations of Hill and Pott in the 1700's. Distinguishing between DNA-reactive chemicals and those which increase cancer risk by increasing cell proliferation has been a major breakthrough in delineating overall mechanisms. Competing processes for activation versus inactivation of chemicals occur at many levels, including metabolism, DNA repair, and cellular repair processes. These processes can be affected by other agents to decrease carcinogenesis (chemoprevention). Increasing knowledge of the multiple steps of carcinogenesis is leading to improved methods for screening chemicals for carcinogenic activity and for regulatory decision making. Improvements in assessment of modes of action involved in animal and *in vitro* models have led to more rational approaches to assessing relevance to humans. The advent of genomics and high-throughput technologies have contributed to investigations of mechanisms and is beginning to impact development of better methods for screening chemicals. Based on developments in basic research, epidemiology, and astute clinical observations, the major risk factors and etiologic agents have been identified for a majority of cancers, which is beginning to lead to methods to decrease cancer incidence overall and identify targets for early detection and treatment.

Key Words: Cell proliferation; DNA reactivity; non-DNA reactivity; carcinogenicity testing; human relevance.

Chemical exposure has been related to the development of cancer ever since the observation by John Hill (Hill, 1761) that snuff users developed nasal cancer more frequently than the general population. However, chemical carcinogenesis generally dates specifically to the observation by Sir Percival Pott (1775) in 1775 describing the frequent occurrence of cancer of the scrotum in chimney sweeps in England. He hypothesized that this was because of their significant exposure to soot. More importantly, he also proposed a mechanism to reduce the incidence of these cancers simply by requiring these individuals to bathe on a regular basis. This was instituted, and the incidence of scrotal cancer was essentially eliminated. It is

important to note, given subsequent scientific discoveries and emphasis on extrapolation to low exposure levels, that he did not recommend eliminating the exposure completely, merely reducing it. Scrotal cancer today is a rare disease.

Astute clinical observations such as that made by Pott (1775) have been the basis for the discovery of many of the currently known classes of chemical carcinogens in humans. Examples include the observation by Rehn (1895) in 1895 that workers in the aniline dye industry in Germany frequently developed bladder cancer and more recent observations concerning the induction of angiosarcomas in patients exposed to contrast material used for radiologic imaging studies (Vajdic *et al.*, 1986) and vinyl chloride exposure in the workplace in Louisville, Kentucky (Creech and Johnson, 1974).

Research based on these observations led to several seminal discoveries in the history of chemical carcinogenesis. Investigation of coal tar, e.g., led to the first experimental induction of tumors in animal models by Yamagiwa and Ichikawa (1915) by painting this material on the skin of rabbits and mice. These models have been used in carcinogenesis research ever since. Similarly, the relationship of soot to cancer induction led to the purification and identification of the first pure chemical carcinogen by Kennaway and Hieger (1930) when they purified a small amount of dibenz[a,h]anthracene and produced tumors by painting the chemical on the backs of mice. The observation by Rehn (1895) of bladder cancer in the aniline dye industry led to the discovery by Kinosita (1936) and Yoshida (1933) of the induction of liver cancer in rats by *o*-aminoazotoluene. This research also demonstrated the importance of dietary effects on the carcinogenic process.

Ultimately, 2-naphthylamine was identified as one of the principle chemicals to which workers in the aniline dye industry were actually exposed, and Hueper *et al.* (1938) demonstrated that it was a bladder carcinogen when administered to dogs. In their study, they were also the first to emphasize the importance of latency. Their experiment involved administration of 2-naphthylamine to dogs for 2 years. The long latency period

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National Library of Medicine Current Catalog National Library of Medicine (U.S.), 1993 Current Catalog National Library of Medicine (U.S.), 1993 First multi year cumulation covers six years 1965 70 Biennial Report (International Agency for Research on Cancer). , 1992 **Toxicology** Hans Marquardt, Siegfried G. Schäfer, Roger O. McClellan, Frank Welsch, 1999-10-05 Toxicology is a comprehensive text for researchers and graduate students in toxicology and public health It addresses every aspect of the field starting with the fundamentals and incorporating such areas as organ toxicology applications and environmental toxicology In addition to covering the traditional subject matter of toxicology special emphasis has been placed on recent areas of interest such as risk assessment apoptosis and methodical developments Key Features Comprehensive text covering all aspects of the field of toxicology Analyzes the importance of toxicokinetics and metabolism as well as cellular targets for the mechanisms of toxic effects Identifies the various classes of chemical compounds responsible for the toxic effects Describes the approaches and methods used by various disciplines which investigate toxic effects and their prevention Adapted from a very successful German text this edition is completely revised and expanded The text is well illustrated with diagrams charts and tables *Lebensmittelsicherheit und Lebensmittelüberwachung* Hartmut Dunkelberg, Thomas Gebel, Andrea Hartwig, 2013-04-12 Expertenwissen f r jedermann Diese Auskopplung aus dem Handbuch der Lebensmitteltoxikologie beschreibt umfassend und kompetent heute verwendeten Methoden und Verfahren der Lebensmittelberwachung **Oxford Textbook of Public Health: Methods of public health** Walter Werner Holland, Roger Detels, 1997 *German books in print* , 1971 **Mitteilungen aus dem Gebiete der Lebensmitteluntersuchung und Hygiene** , 1993

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