Problems in the Evaluation of Carcinogenic Hazard from Use of Food Additives* 

Subcommittee on Carcinogenesis, Food Protection Committee, Food and Nutrition Board, National Academy of Sciences-National Research Council, Washington, D.C. 

(Herbert E. Carter, Chairman; Paul R. Cannon, Charles J. Kessler, Morton L. Levin, James A. Miller, Arthur A. Nelson, and Philippe Shubik) 

(National Academy of Sciences-National Research Council, Washington D.C.)

FOREWORD 

The Food Protection Committee has discussed in a number of its reports general principles and procedures for evaluating the safety of additives for use in providing our food supply. In these statements the problem of evaluating carcinogenic hazard is recognized but not extensively considered. The public attitude and general state of knowledge concerning carcinogenic hazards in the environment seemed to warrant special consideration of carcinogenic hazard associated with use of food additives, and to this end the Food Protection Committee formed its Subcommittee on Carcinogenesis. 

The present report was prepared by the Subcommittee after extensive review of available information. It is a consensus of often widely diverse viewpoints and interpretations. 

CONTENTS

Introduction ........................................ 430 

General Considerations and Principles Underlying Evaluation of Carcinogenic Activity and Hazard . 431 

Definitions ....................................... 431 

Strong and Weak Carcinogens ...................... 432 

Consideration of General Principles ............... 433 

Evaluation of the Carcinogenicity of Food Additives ........................................ 442 

Experimental Animals ................................ 442 

Diet ................................................. 444 

Experimental Procedures ......................... 444 

Procedure for Evaluating Carcinogenicity .......... 447 

Study of Human Populations in Evaluating Carcinogenicity 447 

* This report is a reprint of Publication 749 of the National Academy of Sciences-National Research Council, issued in December, 1959, and copies of this report may be obtained from that organization. It is being reprinted in Cancer Research so that the information contained in it will be available to interested investigators in the field.

The members of the Food Protection Committee, which established the Subcommittee on Carcinogenesis, are as follows: William J. Darby, Chairman; David B. Hand, Vice Chairman; Paul R. Cannon, Herbert E. Carter, Julius M. Coon, George C. Decker, Elliott A. Maynard, Emil M. Mrak, R. Blackwell Smith, Jr., and Henry F. Smyth, Jr.
INTRODUCTION

Food additives as possible factors in the etiology of human cancer must be considered within the framework of our knowledge of causal factors for cancer in general. Since Pott's observation in 1775 that chimney sweeps developed an unusually high incidence of carcinomas of the scrotum, there have been defined a number of other occupational and environmental groups which develop significantly higher incidences of cancers at specific sites than are found in the general population. These groups include workers in the manufacture of certain organic dyes (cancer of the urinary bladder), certain tar and oil workers (skin cancer), chromate refiners (bronchogenic carcinomas), and persons exposed to radium, in particular watch-dial painters and the recipients of radium water as a therapeutic agent (osteogenic sarcomas).

The suspected carcinogen in each of the instances cited (except that of chromate refiners) has induced cancer in laboratory animals similar to that produced in man. For instance, exposure to coal tar gives rise to skin cancer in the rabbit and various other laboratory animals as well as in man. These observations led to the isolation and the synthesis of the first chemically defined carcinogens, 1,2,5,6-dibenzanthracene and 3,4-benzpyrene. Subsequent studies have shown that a large number of related polycyclic aromatic hydrocarbons are also carcinogenic for experimental animals, although most of these compounds are not known to represent present environmental hazards for man. Similarly, the occurrence of cancer of the urinary bladder in workers in the manufacture of certain organic dyes led to attempts to induce similar tumors in experimental animals with β-naphthylamine. Benign tumors of the bladder in rats and rabbits were observed and, eventually, carcinomas in the bladders of dogs treated parenterally or orally for long periods. Although the benign lesions were not considered of critical importance at the time, they gave an early indication of the potential activity of β-naphthylamine. Subsequent studies have revealed the carcinogenicity for the bladder of two related amines both in experimental animals and in man. In like manner, the different cancers seen in men exposed to x-rays and other ionizing radiations have been produced in experimental animals together with other types of cancer not attributable in the human to irradiation.

It has not yet been possible to induce cancer in animals by experimental exposure simulating certain conditions epidemiologically associated with cancer induction in man. For example: Although recent evidence has shown a close correlation between the rising incidence of bronchogenic carcinoma in the United States and Europe and heavy smoking and atmospheric pollution, these tumors have not been observed in experimental animals under conditions intended to simulate the respiratory exposure to tars and soots in man. This apparent lack of correspondence between the epidemiological and experimental findings is not surprising. At the present time about 30,000 cases of bronchogenic carcinoma occur annually in the United States in a population of about 60,000,000 over the age of 40 years. In 25 years this would amount to 750,000,000 cases, a cumulative incidence of about 1.3 per cent in the older adult population. Taking into account recent trends in mortality from lung cancer and other causes, approximately 2.5 per cent of the population may be expected eventually to develop lung cancer. In the laboratory, practical considerations (particularly

1 Throughout this report the term food additive is used as defined by the Food Protection Committee: A food additive is a substance or mixture of substances, other than a basic foodstuff, which is present in food as a result of any aspect of production, processing, storage, or packaging. The term does not include chance contaminants.

2 It should be noted, however, that the expected life-time incidence among male heavy cigarette smokers is estimated to be considerably greater than 2.5 per cent. (Cutler, S. J., and D. B. Loveland. The risk of developing lung cancer and its relationship to smoking. J. Natl. Cancer Inst. 15:201-211, 1954.)
21 (4)


<table>
<thead>
<tr>
<th>Updated version</th>
<th>Access the most recent version of this article at: <a href="http://cancerres.aacrjournals.org/content/21/4.citation">http://cancerres.aacrjournals.org/content/21/4.citation</a></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>E-mail alerts</th>
<th>Sign up to receive free email-alerts related to this article or journal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reprints and Subscriptions</td>
<td>To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at <a href="mailto:pubs@aacr.org">pubs@aacr.org</a>.</td>
</tr>
<tr>
<td>Permissions</td>
<td>To request permission to re-use all or part of this article, contact the AACR Publications Department at <a href="mailto:permissions@aacr.org">permissions@aacr.org</a>.</td>
</tr>
</tbody>
</table>