

1



# *Food Factors*

Proceedings of the 2nd International Conference on Food Factors (ICoFF)

**Editors:**

**Hajime Ohigashi**

**Toshihiko Osawa**

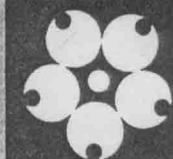
**Junji Terao**

**Shaw Watanabe**

**Toshikazu Yoshikawa**

IOS  
Press  
**OHM**  
Ohmsha





# *Food Factors*

Proceedings of the 2nd International Conference on Food Factors (ICoFF)

**Editors:**

Hajime Ohigashi

Toshihiko Osawa

Junji Terao

Shaw Watanabe

Toshikazu Yoshikawa

IOS  
Press  
  
Ohmsha

© 2000, IOS Press

All rights reserved. No part of this book may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, without the prior written permission from the publisher.

ISBN 1 58603 102 3 (IOS Press)

ISBN 1 58603 107 4 (IOS Press, set of two volumes)

ISBN 4 274 90404 0 C3047 (Ohmsha)

ISBN 4 274 90406 7 C3047 (Ohmsha, set of two volumes)

Library of Congress Catalog Card Number: 00-108978

This is the book edition of the journal *BioFactors*, Volume 12 (2000), ISSN 0951-6433

*Publisher*

IOS Press

Nieuwe Hemweg 6B

1013 BG Amsterdam

The Netherlands

fax: +31 20 620 3419

e-mail: [order@iospress.nl](mailto:order@iospress.nl)

*Distributor in the UK and Ireland*

IOS Press/Lavis Marketing

73 Lime Walk

Headington

Oxford OX3 7AD

England

fax: +44 1865 75 0079

*Distributor in Germany, Austria and Switzerland*

IOS Press/LSL.de

Gerichtsweg 28

D-04103 Leipzig

Germany

fax: +49 341 9954255

*Distributor in the USA and Canada*

IOS Press, Inc.

5795-G Burke Centre Parkway

Burke, VA 22015

USA

fax: +1 703 323 3668

e-mail: [iosbooks@iospress.com](mailto:iosbooks@iospress.com)

*Distributor in Japan*

Ohmsha, Ltd.

3-1 Kanda Nishiki-cho

Chiyoda-ku, Tokyo 101

Japan

fax: +81 3 3233 2426

LEGAL NOTICE

The publisher is not responsible for the use which might be made of the following information.

PRINTED IN THE NETHERLANDS

Proceedings of FOOD FACTORS International Conference  
on Food Factors (ICoFF)

Published in two volumes

Volume 1

# Proceedings of the 2nd International Conference on Food Factors (ICoFF)

Published in two volumes

Volume 1

# Food Factors

Edited by

**Hajime Ohigashi**

*Division of Applied Life Sciences, Graduate School of Agriculture,  
Kyoto University, Kyoto, Japan*

**Toshihiko Osawa**

*Graduate School of Bioagricultural Sciences, Nagoya University,  
Nagoya, Japan*

**Junji Terao**

*Department of Nutrition, School of Medicine, The University of Tokushima,  
Tokushima, Japan*

**Shaw Watanabe**

*Department of Nutritional Sciences, Tokyo University of Agriculture,  
Tokyo, Japan*

and

**Toshikazu Yoshikawa**

*First Department of Internal Medicine,  
Kyoto Prefectural University of Medicine, Kyoto, Japan*



Amsterdam • Berlin • Oxford • Tokyo • Washington, DC

---

# Contents

Preface	1
<b>Novel Aspects of Food Factors</b>	<b>3</b>
<i>P. Talalay</i> Chemoprotection against cancer by induction of Phase 2 enzymes	5
<i>S. Arai</i> Functional food science in Japan: State of the art	13
<i>Z. Dong</i> Effects of food factors on signal transduction pathways	17
<i>S. Kaminogawa</i> Food allergens and the mucosal immune system	29
<b>Minerals and Trace Elements</b>	<b>33</b>
<i>M. Nishimuta</i> The concept of intracellular-, extracellular- and bone-minerals	35
<i>G.F. Combs, Jr.</i> Food system-based approaches to improving micronutrient nutrition: The case for selenium	39
<i>M. Abdulla and P. Gruber</i> Role of diet modification in cancer prevention	45
<i>R. Masuyama and K. Suzuki</i> High phosphorus feeding decreases the expression of renal PTH/PTHrP-receptor mRNA in rats	53
<i>H. Tsuchita, N. Manabe and S. Saito</i> Influence of food ingredients on iron availability	59
<i>M. Komai, T. Goto, H. Suzuki, T. Takeda and Y. Furukawa</i> Zinc deficiency and taste dysfunction; Contribution of carbonic anhydrase, a zinc-metalloenzyme, to normal taste sensation	65
<b>Recent Topics in Cancer Prevention</b>	<b>71</b>
<i>J.H. Weisburger</i> Prevention of cancer and other chronic diseases worldwide based on sound mechanisms	73

<i>H. Tsuda, K. Sekine, N. Takasuka, H. Toriyama-Baba and M. Iigo</i> Prevention of colon carcinogenesis and carcinoma metastasis by orally administered bovine lactoferrin in animals	83
<i>H. Adlercreutz, W. Mazur, K. Stumpf, A. Kilkkinen, P. Pietinen, K. Hultén and G. Hallmans</i> Food containing phytoestrogens, and breast cancer	89
<i>Y. Matsumura, N. Yoshiike, T. Yokoyama and H. Tanaka</i> Dietary intake and cancer mortality in Japan	95
<i>H. Mori, K. Kawabata, K. Matsunaga, J. Ushida, K. Fujii, A. Hara, T. Tanaka and H. Murai</i> Chemopreventive effects of coffee bean and rice constituents on colorectal carcinogenesis	101
<i>Y.-J. Surh, S.S. Han, Y.-S. Keum, H.-J. Seo and S.S. Lee</i> Inhibitory effects of curcumin and capsaicin on phorbol ester-induced activation of eukaryotic transcription factors, NF- $\kappa$ B and AP-1	107
<i>D.M. Shankel, S.P. Pillai, H. Telikepalli, S.R. Menon, C.A. Pillai and L.A. Mitscher</i> Role of antimutagens/anticarcinogens in cancer prevention	113
<i>K. Kikugawa, K. Hiramoto and T. Kato</i> Prevention of the formation of mutagenic and/or carcinogenic heterocyclic amines by food factors	123
<i>K. Watanabe, T. Kawamori, S. Nakatsugi and K. Wakabayashi</i> COX-2 and iNOS, good targets for chemoprevention of colon cancer	129
<b>Peptides and Amino Acids</b>	
<i>M. Smriga, H. Murakami, M. Mori and K. Torii</i> Effects of L-lysine deficient diet on the hypothalamic interstitial norepinephrine and diet-induced thermogenesis in rats <i>in vivo</i>	137
<i>M. Yoshikawa, H. Fujita, N. Matoba, Y. Takenaka, T. Yamamoto, R. Yamauchi, H. Tsuruki and K. Takahata</i> Bioactive peptides derived from food proteins preventing lifestyle-related diseases	143
<i>A.W. Lipkowski, B. Baranowska, E. Marczak, B. Kwiatkowska-Patzer, B. Gajkowska and M. Walski</i> Protein hydrolysates for oral tolerance	147
<i>S.E Kim, H.H. Kim, J.Y. Kim, Y.I. Kang, H.J. Woo and H.J. Lee</i> Anticancer activity of hydrophobic peptides from soy proteins	151
<i>Y. Kawamura, M. Manabe and K. Kitta</i> Antitumor protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling the status of pRb, c-MYC, cyclin E-cdk2, and p21 <sup>WAF1</sup> in the G1/S transition	157



<i>M. Miwa</i>	
Development of functional foods based on physiological activity of amino acids and peptides in Japan	161
<b>Flavones and Flavonols</b>	167
<i>C. Morand, C. Manach, V. Crespy and C. Remesy</i>	
Respective bioavailability of quercetin aglycone and its glycosides in a rat model	169
<i>M.K. Piskula</i>	
Factors affecting flavonoids absorption	175
<i>K. Shimoi, N. Saka, K. Kaji, R. Nozawa and N. Kinae</i>	
Metabolic fate of luteolin and its functional activity at focal site	181
<i>A. Murakami, Y. Nakamura, Y. Ohto, M. Yano, T. Koshiba, K. Koshimizu, H. Tokuda, H. Nishino and H. Ohigashi</i>	
Suppressive effects of citrus fruits on free radical generation and nobiletin, an anti-inflammatory polymethoxyflavonoid	187
<i>M.-H. Siess, A.-M. Le Bon, M.-C. Canivenc-Lavier and M. Suschetet</i>	
Mechanisms involved in the chemoprevention of flavonoids	193
<i>H. Ashida</i>	
Suppressive effects of flavonoids on dioxin toxicity	201
<b>Isoflavones</b>	207
<i>S. Barnes, B. Boersma, R. Patel, M. Kirk, V.M. Darley-USmar, H. Kim and J. Xu</i>	
Isoflavonoids and chronic disease: Mechanisms of action	209
<i>M. Uehara, Y. Arai, S. Watanabe and H. Adlercreutz</i>	
Comparison of plasma and urinary phytoestrogens in Japanese and Finnish women by time-resolved fluoroimmunoassay	217
<i>S. Watanabe, R. Haba, K. Terashima, Y. Arai, T. Miura, H. Chiba and K. Takamatsu</i>	
Antioxidant activity of soya hypocotyl tea in humans	227
<i>S. Watanabe, K. Terashima, Y. Sato, S. Arai and A. Eboshida</i>	
Effects of isoflavone supplement on healthy women	233
<i>H. Kim, H. Xia, L. Li and J. Gewin</i>	
Attenuation of neurodegeneration-relevant modifications of brain proteins by dietary soy	
<i>R. Mackey, A. Ekangaki and J.A. Eden</i>	
The effects of soy protein in women and men with elevated plasma lipids	251

J.E. Trosko and C.C. Chang

Modulation of cell-cell communication in the cause and chemoprevention/chemotherapy of cancer	259
---	-----

<b>Dietary Fibers, Oligosaccharides and Polysaccharides</b>	<b>265</b>
---	------------

M. Nagaoka, H. Shibata, I. Kimura-Takagi, S. Hashimoto, R. Aiyama, S. Ueyama and T. Yokokura

Anti-ulcer effects and biological activities of polysaccharides from marine algae	267
---	-----

M. Mizuno

Anti-tumor polysaccharides from mushrooms during storage	275
--	-----

Y. Sowa and T. Sakai

Butyrate as a model for "Gene-regulating chemoprevention and chemotherapy"	283
--	-----

L. Prosky

When is dietary fiber considered a functional food?	289
---	-----

H. Ishikawa, I. Akedo, T. Nakamura, K. Kimura, Y. Takimoto, T. Suzuki, S. Sato,

Y. Tanaka and T. Otani

Effects of the administration of wheat bran biscuit: Changes in the diet	299
--	-----

A. Schatzkin

Going against the grain? Current status of the dietary fiber-colorectal cancer hypothesis	305
---	-----

Author Index Volumes 1 and 2

313

## Preface

These two volumes of "Food Factors" contain the proceedings of the 2nd International Conference on Food Factors (2nd ICoFF).

Inheriting the success of the 1995 International Conference on Food Factors (ICoFF) at Hamamatsu, Japan, the 2nd ICoFF was held from December 12 through 17, 1999 in Kyoto, Japan. The old historical city of Kyoto, with an astounding seventeen UNESCO world cultural heritage sites, attracted scientists from eighteen countries all over the globe and offered an excellent environment to present and discuss topical science in a congenial atmosphere. While in Hamamatsu discussion was centered on food factors for cancer prevention, the 2nd ICoFF covered a wide scope of research on food factors of a variety of physiological significance. The actual goal of the conference was to establish a role of food factors in disease prevention and health promotion from the scientific base.

The proceedings of the conference present recent research data and review lectures by numerous experts and will be of special interest and relevance to all who are concerned with food factors in disease prevention and health promotion. A great deal of the contributions has been selected for publication as the most informative mini-reviews or original research reports. These include recent topics in cancer prevention and antioxidants as well as vitamin E, minerals and trace elements, peptide and amino acids, flavones and flavonols, isoflavones, dietary fibers, oligo- and polysaccharides, lipids, catechins, carotenoids, polyphenols, terpenoids and sulfur-containing compounds.

We would like to take this opportunity to thank the authors for their excellent contributions and cooperation in the development of these proceedings. We would also like to thank the many others whose support made the conference a success.

Tokushima, July 2000

Hajime Ohigashi

Toshihiko Osawa

Junji Terao

Shaw Watanabe

Toshikazu Yoshikawa

Novel Aspects of Food Factors



## Novel Aspects of Food Factors

These two volumes of "Food Factors" contain the proceedings of the 2nd International Conference on Food Factors (2nd ICFF).

Inheriting the success of the 1985 International Conference on Food Factors (ICFF) at Hamamatsu, Japan, the 2nd ICFF was held from December 12 through 17, 1992 in Kyoto, Japan. The old historical city of Kyoto, with an astounding seventeen UNESCO world cultural heritage sites, attracted scientists from eighteen countries all over the globe and offered an excellent environment to present and discuss topical sciences in a congenial atmosphere. While in Hamamatsu discussion was centered on food factors for cancer prevention, the 2nd ICFF covered a wide scope of research on food factors of a variety of physiological significance. The actual goal of the conference was to establish a role of food factors in disease prevention and health promotion from the scientific basis.

The proceedings of the conference present recent original data and review lectures by numerous experts and will be of special interest and relevance to all who are concerned with food factors in disease prevention and health promotion. A great deal of the information has been selected for publication as the most informative mini-reviews, original research reports. These include recent topics in cancer prevention and antioxidants as well as vitamin E, minerals and trace elements, protein and amino acids, flavonoids and polyphenols, carotenoids, dietary fibers, oligo- and polysaccharides, lipids, catechins, isoflavones, polyphenols, terpenoids and sulfur-containing compounds.

We would like to take this opportunity to thank the authors for their excellent contributions and cooperation in the development of these proceedings. We would also like to thank the many others whose support made the conference a success.

Osamu Nishimura, 1993

Yoshio Nishimura, 1993

Yoshio Nishimura, 1993

Yoshio Nishimura, 1993

the ability of reactions that serve to protect cells against the toxicities of xenobiotics and carcinogens. Phase 1 enzymes are involved in the metabolism of many carcinogens and are induced by a variety of agents. Phase 2 enzymes are involved in the conjugation of the products of Phase 1 metabolism with endogenous or exogenous molecules, thereby facilitating their excretion. Phase 3 enzymes are involved in the transport of the conjugates out of the cell. The induction of Phase 1 and Phase 2 enzymes is a key event in the carcinogenic process, and the study of these enzymes is important for understanding the mechanisms of carcinogenesis and for developing strategies for cancer prevention and treatment.

**2. Regulation of Phase 1 and Phase 2 Enzymes**

Phase 1 and Phase 2 enzymes are regulated by a variety of factors, including hormones, growth factors, and environmental agents. The regulation of these enzymes is complex and involves multiple levels of control. Phase 1 enzymes are primarily regulated at the transcriptional level, while Phase 2 enzymes are regulated at both the transcriptional and translational levels. The induction of Phase 1 and Phase 2 enzymes is a key event in the carcinogenic process, and the study of these enzymes is important for understanding the mechanisms of carcinogenesis and for developing strategies for cancer prevention and treatment.

## Mini-review

# Chemoprotection against cancer by induction of Phase 2 enzymes

Paul Talalay

*Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205, USA*

*Tel.: +1 410 955 3499; Fax: +1 410 502 6818; E-mail: ptalalay@jhmi.edu or ptalalay@aol.com*

**Abstract.** Induction of Phase 2 enzymes is an effective and sufficient strategy for achieving protection against the toxic and neoplastic effects of many carcinogens. It is proposed that the concept of Phase 2 enzymes as being responsible only for the conjugation of functionalized xenobiotics with endogenous cellular ligands such as glutathione (glutathione S-transferases) and glucuronic acid (UDP-glucuronosyltransferases) be expanded to include proteins with the following common characteristics: (a) coordinate induction by a broad range of chemical agents that all have the capacity to react with sulfhydryl groups; (b) possible regulation by common promoter elements; and (c) catalysis of reactions that lead to comprehensive protection against electrophile and reactive oxygen toxicities, by a wide variety of mechanisms. These mechanisms include: conjugation with endogenous ligands, chemical modification of reactive features of molecules that can damage DNA and other macromolecules, and generation or augmentation of cellular antioxidants. In addition to the above conjugating enzymes, a provisional and partial list of Phase 2 proteins might include: NAD(P)H:quinone reductase, epoxide hydrolase, dihydrodiol dehydrogenase,  $\gamma$ -glutamylcysteine synthetase, heme oxygenase-1, leukotriene B<sub>4</sub> dehydrogenase, aflatoxin B<sub>1</sub> dehydrogenase, and ferritin.

**Keywords:** Glutathione transferase, glutathione, NAD(P)H:quinone reductase, heme oxygenase,  $\gamma$ -glutamylcysteine synthetase, epoxide hydrolase, ferritin, electrophile toxicity, redox cycling, antioxidants, reactive oxygen species

## 1. History and evolution of the Phase 1 and Phase 2 enzyme concept

More than 30 years ago R.T. Williams [42] of Saint Mary's Hospital Medical School in London formally suggested that the metabolism of xenobiotics could be viewed as resulting from sequential actions of two families of enzymes: Phase 1 enzymes that catalyze "asynthetic" reactions, which functionalize compounds largely through oxidations and reductions, and Phase 2 enzymes which promote "synthetic" conjugations of Phase 1 products with endogenous ligands such as glutathione (GSH), glucuronic and amino acids, leading usually to more water-soluble and more easily excretable products. Much subsequent work has established that the enzymes belonging to the two groups are induced by a wide variety of synthetic and natural chemical agents, and are regulated by distinct and separate mechanisms.

This somewhat limited view of the nature and functions of Phase 2 enzymes (i.e., synthesis of conjugates) is gradually giving way to a much broader concept of their scope and importance. The notion is evolving that they should perhaps be defined by the following properties: (a) coordinate induction by many types of inducers that also induce classical Phase 2 enzymes such as glutathione S-transferases (GSTs); (b) regulation by mechanisms that are very similar and may involve common promoter elements (e.g., the Antioxidant Responsive Element, or ARE) [13,32]; and (c) catalysis of a

wide variety of reactions that serve to protect cells against the toxicities of electrophiles and reactive oxygen species by converting them into less toxic products [14,35,37]. Indeed, there is now extensive evidence that Phase 2 enzymes not only provide a major mechanism by which cells combat the toxicities of electrophiles and reactive oxygen species, but that their induction is a highly effective and sufficient condition for protecting cells against the toxic and neoplastic challenges of many types of carcinogens. It is therefore not surprising that the discovery that many edible plants contain substantial quantities of potent Phase 2 enzyme inducers has stimulated great interest in utilizing such plants, and their inducer components, to achieve protection against cancer [9,29,43,44]. This paper reviews evidence that supports these suggestions for a broader role of Phase 2 enzymes and their important participation in protection against cancer and electrophile toxicity.

## 2. Roles of Phase 1 and Phase 2 enzymes in carcinogenesis and protection against cancer

A critical advance in understanding the mechanisms of carcinogenesis was the recognition by James and Elizabeth Miller [17] that most carcinogens are quite unreactive and innocuous procarcinogens, which require conversion by cellular (Phase 1) enzymes to highly reactive, electrophilic, ultimate carcinogens that react directly with nucleophilic centers of macromolecules such as DNA, to produce a series of damaging events that can evolve into cancer. These workers also demonstrated that Phase 1 enzymes were inducible, and that their activities often gave rise to nonelectrophilic detoxication products. Both electrophilic and nonelectrophilic products of Phase 1 enzyme activities are substrates for Phase 2 enzymes, which are likewise inducible, and promote detoxication reactions. Consequently the outcome of carcinogen exposure is controlled in large part by the balance between Phase 1 enzymes that can generate ultimate carcinogens and Phase 2 enzymes that detoxify these products. Although these families of enzymes are under genetic and hormonal control, they are also regulated by inducers, and the shifting of this balance by induction toward the dominance of Phase 2 enzymes has emerged as an important strategy for achieving chemoprotection against electrophile toxicity and malignancy.

An important milestone in research on chemoprotection against cancer was the discovery by Wattenberg (see reviews [38,39]) that the phenolic antioxidants BHA and BHT could substantially reduce the development of a variety of tumors evoked by numerous carcinogens in rodent models. Since these antioxidants are widely used as food preservatives, these discoveries suggested for the first time that cancer could be blocked by agents already in the food chain, and therefore presumably of relatively low toxicity. Our early biochemical and molecular studies [1–3] disclosed that administration of these antioxidants to rodents evoked marked changes in the metabolism of carcinogens and that these changes were attributable to elevation of the specific activities of Phase 2 enzymes: glutathione transferases (GSTs), epoxide hydrolase, and NAD(P)H:quinone reductase (QR) in the livers and peripheral tissues [1–3]. Furthermore, more detailed analysis, including mRNA measurements, established that these elevations resulted from enhanced rates of gene transcription and enzyme synthesis [20].

Inducers of Phase 2 enzymes are of two types: monofunctional and bifunctional [30]. Polycyclic aromatics, azo dyes, dioxin, and flavones (all large planar aromatics) are bifunctional in that they induce both Phase 2 and certain Phase 1 enzymes. These bifunctional agents bind with high affinity to the *Ah* (Aryl hydrocarbon) receptor and induce several cytochromes P450 that may activate carcinogens, e.g. CYP1A1 and 1A2. The induction of Phase 1 enzymes is mediated by the *Ah* receptor or the gene products under its control. In contrast, monofunctional inducers have no common structural features (see below), induce Phase 2 enzymes without significantly elevating Phase 1 enzymes, and are independent of *Ah* receptors or their functions [30]. One important consequence of this dichotomy of inducer types



is that it focuses on both the desirability and practicality of selecting monofunctional inducers as agents for achieving chemoprotection, thereby minimizing the hazards of activating carcinogens.

### 3. Determination of potencies of Phase 2 enzyme inducers

Recognition of the importance of Phase 2 enzyme induction as a mechanism of chemoprotection suggested the need to devise methods for detecting and quantifying the inducer potencies of pure chemicals and of extracts of natural products. Quinone reductase (QR) was selected as a convenient target enzyme, because of its coordinate induction with other Phase 2 enzymes, wide distribution in mammalian tissues, large inducer response, and ease of measurement by a coupled tetrazolium dye reduction assay. A robust and highly useful murine hepatoma cell line (Hepa 1c1c7) grown in 96-well microtiter plate wells provided a simple system for the highly reproducible quantitative assays of inducer potencies of single compounds, mixtures, or of plant extracts [9,28,29]. The results obtained from this system have reliably predicted the behavior of inducers in animal systems. Furthermore, the availability of mutant Hepa cells defective in cytochrome P-450 activity or aryl hydrocarbon receptor function has provided a simple method for making the important distinction between monofunctional and bifunctional inducers [30]. Potencies of inducers, conveniently expressed as concentrations required to double the QR activity, have been found to vary by 5 orders of concentration magnitudes [22,23].

### 4. Chemical characteristics of monofunctional Phase 2 enzyme inducers

Important insight into the chemical nature of inducers emerged from studies of analogues of the widely used food antioxidant BHA [27]. They pointed to *tert*-butylhydroquinone, a metabolite of BHA, as the active inducer, and showed that demethylation to phenols was required for induction. The orientations of the hydroxyl groups of these diphenols were critical. Only 1,4-diphenols (hydroquinones) and 1,2-diphenols (catechols), both of which are readily oxidizable to quinones, were inducers, whereas 1,3-diphenols (resorcinols) which are not oxidizable were inactive. Other substituents on the aromatic rings had little effect on inducer potency. Although oxidizability was clearly required for inducer activity, these experiments did not disclose whether the quinone products were the ultimate inducers or whether the redox process (possibly generating reactive oxygen species) produced the signals for induction. This issue was resolved by the demonstration that many Michael reaction acceptors (i.e., olefins or acetylenes conjugated to electron-withdrawing groups) were efficient inducers and that their inducer potencies correlated closely with their Michael reactivity [36]. This generalization not only explained the inducer activities of many compounds, but also permitted the correct prediction of inducer properties of novel structures. Since quinones are excellent Michael acceptors, we ascribed the inducer properties of BHA and its diphenol metabolite to their ability to undergo oxidations to quinones.

Subsequently, many different types of monofunctional inducers have been recognized. In addition to oxidizable diphenols and phenylenediamines, quinones and other Michael reaction acceptors, the range of inducers includes: isothiocyanates and their thiol addition products (e.g., dithiocarbamates); 1,2-dithiole-3-thiones; trivalent arsenicals; heavy metals such as mercury and cadmium; hydroperoxides; and vicinal dimercaptans [22,23]. More recently certain carotene metabolites have also been shown to be inducers [15]. Although these classes of inducers appear to have few common properties, they are all chemically reactive. They include many electrophiles, a single class of nucleophiles, as well as powerful oxidants and antioxidants. All inducers can modify sulfhydryl groups either by alkylation or by redox