edited by J. RYDSTRÖM
J. MONTELIUS
and M. BENGTSSON

# EXTRAHEPATIC DRUG METABOLISM AND CHEMICAL CARCINOGENESIS

**ELSEVIER** 

## EXTRAHEPATIC DRUG METABOLISM AND CHEMICAL CARCINOGENESIS

Proceedings of the International Meeting on Extrahepatic Drug Metabolism and Chemical Carcinogenesis held in Stockholm, Sweden, on 17-20 May, 1983

Editors

Jan Rydström

Johan Montelius

and

Margot Bengtsson





1983



ELSEVIER SCIENCE PUBLISHERS AMSTERDAM · NEW YORK · OXFORD

#### © 1983 Elsevier Science Publishers B.V.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the copyright owner.

ISBN 0-444-80538-9

Published by: Elsevier Science Publishers B.V. P.O. Box 211 1000 AE Amsterdam, The Netherlands

Sole distributors for the USA and Canada: Elsevier Science Publishing Company Inc. 52 Vanderbilt Avenue New York, N.Y. 10017

#### **FOREWORD**

The tremendous progress which has characterized toxicological research during the last two decades has involved mainly research on hepatic systems. In depth characterization of isolated proteins, e.g., cytochrome P-450, has provided powerful tools for the elucidation of the mechanisms of action of drug-metabolizing systems and has allowed conclusions to be drawn which may also apply to extrahepatic systems. Based on this knowledge, hypotheses for metabolic activation and chemical carcinogenesis in general have been advocated which have been questioned only rarely. Epidemiological evidence indicates that more than 95% of all human cancers in the Western world are extrahepatic and that up to 80% of these are related to diet, environmental factors, and, indirectly, endogenous factors. Obviously, there is a need for more extensive research on the relationship between cancer in a specific extrahepatic organ and the generation of potential carcinogens and other relevant processes in that organ. The logical approach is thus to use our extensive knowledge of the hepatic system as a platform.

The International Meeting on Extrahepatic Drug Metabolism and Chemical Carcinogenesis held in Stockholm, 17-20 May 1983, from which the present proceedings are derived, was the first meeting which has specifically addressed the problems and approaches peculiar to extrahepatic carcinogenesis. Topics included characterization and regulation of cytochrome P-450 and other detoxication enzymes, DNA-adduct formation and repair, and model systems of extrahepatic carcinogenesis. The success of the meeting and the exceptionally good response from lecturers and other participants indicates the importance of stressing the often unique problems in extrahepatic carcinogenesis. A second meeting on similar topics is therefore planned to take place in USA in 1986.

#### Scientific Advisory Committee

P.L. Grover

J.-A. Gustafsson

C.F. Jefcoate

D.W. Nebert

S. Orrenius

J. Rydström

#### CONTENTS

-			-	
D	m	0	- 3	CP
$\Gamma$	1			(-

COMPARATIVE ASPECTS OF EXTRAHEPATIC AND HEPATIC DRUG METABOLISM AND CHEMICAL CARCINOGENESIS	
Selectivity of lesions produced by 7,12-dimethylbenz[ <u>a</u> ]anthracene in rat Charles Huggins	3
Initiation of carcinogenesis with chemicals - a biological per- spective Emmanuel Farber	11
Differences between kidney and liver in the regulation of micro- somal testosterone hydroxylase activities in inbred mice Roy Hawke, Lynn Raynor, Gurmit Singh and Allen Neims	23
The role of rabbit cytochrome P-450, form 5, in the pulmonary and hepatic metabolism of aromatic amines to mutagenic products Iain G.C. Robertson, Tore Aune, Cosette J. Serabjit-Singh, Jane E. Croft, John R. Bend and Richard M. Philpot	25
Comparison of coumarin 7-hydroxylase activities in kidney and liver of DBA/2J and C57BL/6J mice Pekka Kaipainen, Daniel W. Nebert and Matti Lang	27
Effect of various solvents on the xenobiotic biotransformation in the liver and the kidneys of the rat: a comparative study Tuula Heinonen, Eivor Elovaara, Säde Laurén, Harri Vainio and Jorma Järvisalo	29
Profile of drug metabolizing enzymes in the nuclei and microsomes of hepatic and extrahepatic tissues from monkeys Gian Maria Pacifici and Anders Rane	33
Comparative kinetic aspects of aromatics metabolism by rabbit lung and rat liver microsomes Dmitriy I. Metelitza, Sergey A. Usanov, Alexander N. Eriomin and Irina V. Tishchenko	39
MULTIPLICITY, REGIOSPECIFICITY AND LEVELS OF P-450, EPOXIDE HYDRO- ASE AND CONJUGATING ENZYMES IN DIFFERENT TISSUES	
Modulation of the levels of cytochrome P-450 isozymes in rabbit	
Barbara A. Domin, Richard M. Philpot, Betty L. Warren and Cosette J. Serabjit-Singh	43

racterization of purified cytochrome P-450 in the rat lung Minro Watanabe, Ikuko Sagami and Tetsuo Ohmachi	51
dence for the presence and reactivity of multiple forms of cyto- chrome P-450 in colonic microsomes from rats and humans Henry W. Strobel, S.N. Newaz, Wan-Fen Fang, Paul P. Lau, R.J. Oshinsky, Daniel J. Stralka and Fred F. Salley	57
racterization of cytochrome P-450 in the rat ventral prostate Tapio Haaparanta, James Halpert, Lena Haglund, Hans Glaumann and Jan-Åke Gustafsson	67
alization of carcinogen-metabolizing enzymes in human and animal tissues Jeffrey Baron, Thomas T. Kawabata, Jan A. Redick, Shirley A. Knapp, Donald G. Wick, Robert B. Wallace, William B. Jakoby and F. Peter Guengerich	73
unohistochemical evidence for a heterogeneous distribution of NADPH-cytochrome P-450 reductase in the rat and monkey brain Lena Haglund, Christer Köhler, Tapio Haaparanta, Menek Gold- stein and Jan-Ake Gustafsson	89
rosomal and cytosolic epoxide hydrolases: total activities, sub- cellular distribution and induction in the liver and extra- hepatic tissues Joseph W. DePierre, Johan Meijer, Winnie Birberg, Åke Pilotti, Lennart Balk and Janeric Seidegård	95
abolism of chemical carcinogens by prostaglandin H synthase T.E. Eling, G.A. Reed, J.A. Boyd, R.S. Krauss and K. Sivarajah	105
staglandin synthase catalyzed metabolism of p-phenetidine to reactive products Peter Moldéus, Roger Larsson, David Ross, Bo Andersson, Magnus Nordenskjöld, Anver Rahimtula and Björn Lindeke	113
roxidase-dependent covalent binding of 7,12-dimethylbenz(a)- anthracene metabolites to rat adrenal microsomes Johan Montelius and Jan Rydström	123
civation of the organospecific carcinogen, methylazoxymethanol, via dehydrogenase enzymes: prevention of colon tumorigenesis in rats and human studies  Morris S. Zedeck, Martin Lipkin and Queng Hui Tan	131
e role of extrahepatic and hepatic sulfation and glucuronidation in chemical carcinogenesis: an overview  Gerard J. Mulder and John H.N. Meerman	143
ecies and tissue differences in the occurrence of multiple forms of rat and human glutathione transferases Bengt Mannervik, Claes Guthenberg, Helgi Jensson, Margareta Warholm and Per Ålin	153

Identification of novel glutathione S-transferases in kidney and lung and the inducibility of various isozymes in liver and other organs F. Oesch, U. Milbert, T. Friedberg and C.R. Wolf	
	163
Isozymes of glutathione transferase in rat testis Claes Guthenberg, Per Alin, Ing-Mari Astrand, Süha Yalçin and Bengt Mannervik	171
Peroxisome proliferation, fatty acid β-oxidation and cancer initia- tion by phenoxyacetic acid herbicides H. Vainio, E. Hietanen, K. Linnainmaa and E. Mäntylä	177
Induction of extrahepatic glutathione S-transferases and NAD(P)H: quinone reductase by anticarcinogenic hindered phenols, lactones and Sudan III	
Mary J. de Long, Hans J. Prochaska and Paul Talalay	181
Glutathione and GSH-dependent enzymes in the human gastric mucosa Claus-Peter Siegers, Renate Hoppenkamps, Ernst Thies and Maged Younes	102
Extrahenatic distribution of microscome and the state of	183
Extrahepatic distribution of microsomal glutathione transferase in the rat Ralf Morgenstern and Joseph W. DePierre	185
Inhibitors for identification of glutathione transferase subunits in the rat	100
Süha Yalçin, Helgi Jensson and Bengt Mannervik	187
A comparison of the glutathione transferases (GST) of three extrahepatic organs with different functions - the adrenal, the lactating mammary gland and the male reproductive system D.J. Meyer, L.G. Cristodoulides, O. Nyan, R. Schuster Bruce and B. Ketterer	189
Glutathione transferase in human brain	109
Maria Olsson, Claes Guthenberg and Bengt Mannervik	191
Non-microsomal activation of styrene to styrene oxide	131
Giorgio Belvedere, Francesco Tursi and Harri Vainio	193
Biotransformation of ethylloflazepate (Victan) in plasma and rat tissues	130
Horace Davi, Eric Marti, Andree Bondon and Werner Cautreels	201
Metabolism of promutagens to ultimate mutagens by the rat ventral prostate and covalent binding of benzo(a)pyrene to prostatic microsomal proteins	
Peter Söderkvist, Leif Busk, Rune Toftgård and Jan-Åke Gustafs- son	
The metabolic activation of AFD	205
The metabolic activation of $AFB_1$ in rat and man Simon Plummer, Alan R. Boobis, Clare Kahn and Donald S. Davies	207

Drug metabolizing enzymes in resting human lymphocytes Janeric Seidegård and Joseph W. DePierre	209
Covalent binding of benzo(a)pyrene to cytochrome P-448 and other proteins in reconstituted mixed function oxidase systems Cecilia Schelin, Bengt Jergil and James Halpert	211
The dose dependent metabolism of anethole, estragole and p-propyl- anisole in relation to their safety evaluation Susan A. Sangster, John Caldwell, Andrew Anthony, Andrew J. Hutt and Robert L. Smith	213
DT-diaphorase in mouse epidermis, induction of the enzyme by methyl- cholanthrene Olve Rømyhr, Vemund Digernes and Olav Hilmar Iversen	215
Inhibition of xenobiotic and steroid metabolism by aminoglutethi- mide in human placentas from smoking and non-smoking mothers Markku Pasanen and Olavi Pelkonen	217
Metabolic conversion of styrene to styrene glycol in the mouse. Occurence of the intermediate styrene-7,8-oxide Marianne Nordqvist, Elisabeth Ljungquist and Agneta Löf	219
Subcellular distribution of epoxide hydrolase activity in the liver, lung, kidney and testis of the C57 Bl male mouse Johan Meijer, Winnie Birberg, Ake Pilotti and Joseph W. DePierre	221
Effect of polychlorinated naphthalenes and biphenyls on polysub- strate monooxygenase and UDP-glucuronosyltransferase activities in rat lung Eero Mäntylä, Antero Aitio and Markku Ahotupa	223
Comparison of the patterns of benzo(a)pyrene conjugates formed in vivo in the liver and kidney of the Northern pike (Esox lucius) Lennart Balk, Susanne Månér and Joseph W. DePierre	225
Does human placental PAH metabolism protect the conceptus? David K. Manchester, Natalie B. Parker, Karen Gottlieb and C. Michael Bowman	227
Separation of multiple forms of cytochrome P-450 from rabbit kidney cortex microsomes Masamichi Kusunose, Kiyokazu Ogita, Emi Kusunose, Satoru Yamamoto and Kosuke Ichihara	229
Cytochrome P-450 from intestinal microsomes of rabbits treated with 3-methylcholanthrene Kosuke Ichihara, Kiyomi Ishihara, Emi Kusunose, Masatoshi Kaku and Kiyokazu Ogita	231
Aryl hydrocarbon hydroxylase (AHH) activity in human placenta and its relation with air pollution Filiz Hincal	233

Mechanisms of extrahepatic bioactivation of aromatic amines: the role of hemoglobin in the N-oxidation of 4-chloroaniline Ines Golly and Peter Hlavica	235
Bio-alkylation of benzo(a)pyrene in rat lung and liver James W. Flesher, Kevin H. Stansbury, Abdelrazak M. Kardy and Steven R. Myers	237
Urinary metabolite patterns as indicators of activation and in- activation reactions in the biotransformation of m-xylene and ethylbenzene Eivor Elovaara, Kerstin Engström and Harri Vainio	239
Dimethylsulfoxide induced activation of renal microsomal ethoxy- coumarin O-deethylation Aniti Zitting, Sinikka Vainiotalo and Eivor Elovaara	241
Drug-metabolizing enzymes in <i>Drosophila melanogaster</i> in relation to genotoxicity testing Aalbert J. Baars, Marijke Jansen and Douwe D. Breimer	243
Enhancement of extrahepatic drug metabolism by phenoxyacid herbi- cides and clofibrate Markku Ahotupa, Eino Hietanen, Eero Mäntylä and Harri Vainio	245
Characterization of epoxide hydrolase from the human adrenal gland Dimitrios Papadopoulos, Janeric Seidegård, Antonis Georgellis and Jan Rydström	247
Genetic variation and regulation of the cytochrome P-450 system in the fruit fly, <i>Drosophila melanogaster</i> Inger Hällström and Agneta Blanck	249
Inhibition of rat lung cytochrome P-450 by chloramphenicol Birgitta Näslund, Ingvar Betner and James Halpert	251
Immunochemical and biochemical evidence of the presence of cyto- chrome P-450 monooxygenase components in rabbit heart and aorta	
Cosette J. Serabjit-Singh, Barbara A. Domin, John R. Bend and Richard M. Philpot	253
INTESTINAL METABOLISM AND ENTEROHEPATIC CIRCULATION OF CARCINOGENS	
Enterohepatic circulation and catabolism of mercapturic acid pathway metabolites of naphthalene Jerome Bakke, Craig Struble, Jan-Ake Gustafsson and Bengt Gustafsson	257
Disposition and metabolism of mutagens-carcinogens in vivo - involvement of the intestinal microflora J. Rafter, L. Möller, L. Nilsson, L. Ball, I. Brandt, G. Larsen, M. Blomstedt, B. Gustafsson and JA. Gustafsson	267

Enterohepatic circulation of the aromatic hydrocarbons benzo(a)-	
pyrene and naphthalene P.C. Hirom, J.K. Chipman, P. Millburn and M.A. Pue	275
Xenobiotics, the intestinal flora, and carcinogenesis Rory P. Remmel and Peter Goldman	283
Studies with amaranth and ouabain in germfree rats David Hewick and Sylvia Wilson	293
Metabolism of 1-nitropyrene in germ-free and conventional rats: role of the gut flora in generation of mutagenic metabolites L.M. Ball, J.J. Rafter, JA. Gustafsson, B.E. Gustafsson and J. Lewtas	295
Kinetic aspects of 2-acetylaminofluorene uptake, metabolism, excretion and enterohepatic circulation Lennart C. Eriksson, Joann Spiewak, Waheed Roomi and Emmanuel Farber	297
The metabolism of benzo(a)pyrene in the intestine and the effect of dietary fats Jon D. Gower and E.D. Wills	299
Effect of diethyl maleate pretreatment on glutathione levels in stomach, liver and blood of rats treated with gastric damage inducing agents Paolo Di Simplicio, Antonella Naldini and Maria Teresa Bianco	303
Effect of cholesterol on phenobarbital inducibility of biotrans- formation enzymes in the small intestinal mucosa and liver of the rat Eino Hietanen and Markku Ahotupa	305
Xenobiotic metabolism in the small intestinal mucosa of children Eino Hietanen, Tuula Heinonen, Marja-Liisa Ståhlberg and Markku Mäki	307
Inhibition of the mutagenic activity of 2-amino-3-methylimidazo- (4,5-f)quinoline (IQ) by rat intestinal mucosa Giovanna Caderni, Maura Lodovici and Piero Dolara	309
The effect of high fat diet on the disposition of benzo(a)pyrene in the gut Susan Bowes and Andrew G. Renwick	311
The cytostatic hexamethylmelamine, administered orally to rats, is metabolized in the liver and the gut wall Pierre Klippert, Paul Borm, Abram Hulshoff, Marie-José Mingels, Gerard Hofman and Jan Noordhoek	315
Biotransformation of hexamethylmelamine in rat isolated intestinal epithelial cells and hepatocytes. Role of mitochondrial cytochrome P-450 Paul Borm, Pierre Klippert, Marie-José Mingels, Abram Hulshoff Ank Frankhuijzen-Sierevogel and Jan Noordhoek	319

	XIII
PITUITARY CONTROL AND ROLE OF CYTOCHROME P-450 IN ENDOCRINE ORGANS	
Metabolism of polycyclic hydrocarbons in the mammary gland and the hormone mimetic action of the carcinogens Thomas L. Dao, Charles E. Morreal and Dilip K. Sinha	325
Benzo(a)pyrene reproductive toxicity and ovarian metabolism Donald R. Mattison, Maria S. Nightingale, Ken Takizawa, Ellen K. Silbergeld, Haruhiko Yagi and Donald M. Jerina	337
Hormonal regulation of cytochrome P-450 dependent monooxygenase activity and benzopyrene metabolism in rat testes I.P. Lee, K. Suzuki, J. Nagayama, H. Mukhtar and J.R. Bend	351
Regulation of the metabolism of 7,12-dimethylbenz(a)anthracene in the rat ovary by gonadotropins Margot Bengtsson, Donald R. Mattison and Jan Rydström	363
Effects of ACTH on metabolism and toxicity of 7,12-dimethylbenz(a)- anthracene in cultured rat adrenal cells Einar Hallberg and Jan Rydström	371
Are pituitary factors acting as modifiers of liver carcinogenesis in the rat? Agneta Blanck, Tiiu Hansson, Lennart Eriksson and Jan-Ake Gustafsson	373
Feminization of hepatic xenobiotic metabolism by ectopic pituitary grafts or by continuous infusion of human growth hormone in male rats  Agneta Blanck, Anders Aström, Tiiu Hansson, Joseph W. DePierre	
and Jan-Ake Gustafsson	375
RECEPTORS AND INDUCTION OF DRUG-METABOLIZING ENZYMES	
Several P-450 genes regulated by the Ah receptor Daniel W. Nebert, Robert H. Tukey, Peter I. Mackenzie, Masahiko Negishi and Howard J. Eisen	379
The Ah receptor: species and tissue variation in binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin and carcinogenic aromatic hydrocarbons	
Allan B. Okey, Michelle E. Mason and Lynn M. Vella Soluble receptor proteins in control of gene expression	389
Jan-Ake Gustafsson, Örjan Wrange, Lorenz Poellinger, Johan Lund, Farhang Payvar and Keith Yamamoto	401
Is the primary function of the $Ah$ locus to regulate cytochrome P-450? Joyce C. Knutson and Alan Poland	400

Molecular biology of cytochrome P-450 Ronald N. Hines, Edward Bresnick, Curtis Omiecinski and Joan Levy	419
Bone marrow toxicity induced by oral benzo[a]pyrene: protection resides at the level of the intestine and liver Catherine Legraverend, David E. Harrison, Francis W. Ruscetti and Daniel W. Nebert	423
Assignment of the Ah locus to mouse chromosome 17 Sirpa O. Kärenlampi, Catherine Legraverend, Peter A. Lalley, Christine A. Kozak and Daniel W. Nebert	425
DRUG METABOLISM, DNA-ADDUCT FORMATION AND DNA REPAIR	
Metabolism and activation of polycyclic hydrocarbons in mammary and other tissue P.L. Grover, D.H. Phillips, C.S. Cooper, W.H. Swallow, A. Weston, P. Vigny, M. O'Hare, A.M. Neville and P. Sims	429
7,12-dimethylbenz[a]anthracene-DNA interactions in mouse embryo cell cultures and mouse skin Anthony Dipple, Josef T. Sawicki, Robert C. Moschel and C. Anita H. Bigger	439
A kinetic approach to polycyclic hydrocarbon activation Colin R. Jefcoate, Maro Christou, Gabriela M. Keller, Chri- stopher R. Turner and Neil M. Wilson	449
In vivo metabolism of benzo(a)pyrene: formation and disappearance of BP-metabolite-DNA adducts in extrahepatic tissues versus liver Marshall W. Anderson and John R. Bend	459
Spectroscopic studies of benzo(a)pyrene-7,8-dihydrodio1-9,10- epoxides covalently bound to DNA Bengt Jernström, Per-Olof Lycksell, Astrid Gräslund, Anders Ehrenberg and Bengt Nordén	469
Kinetics of DNA adduct formation and removal in liver and kidney of rats fed 2-acetylaminofluorene Miriam C. Poirier, John M. Hunt, B'Ann True and Brian A. Laishes	479
Metabolism of azo and hydrazine derivative to reactive intermediates R.A. Prough, M.I. Brown, C.A. Amrhein and L.J. Marnett	489
A role for active oxygen-induced DNA damage in tumor promotion Peter Cerutti, Joseph Friedman and Robert Zimmerman	499
Aromatic amine induced DNA damage in mouse hepatocytes Mona Møller, Irene B. Glowinski and Snorri S. Thorgeirsson	507

Possible significance of a direct interaction between NAD(P)H and N-acetoxy-2-aminofluorene on the binding to human lympho-cyte DNA Janeric Seidegård and Ronald W. Pero	509
Guanosine and deoxyguanosine adducts of nitrogen mustards and ethyleneimines - formation and destruction Kirsti Savela, Seija Kallama and Kari Hemminki	511
A sensitive reversed-phase H.P.L.C. method for the determination of RNA contamination in the analysis of DNA-carcinogen interactions Keith R. Huckle	513
DNA repair as a determining factor in the transplacental organotropic effect of N-methyl-N-nitrosourea Alexei J. Likhachev, Valerii A. Alexandrov, Vladimir N. Anisimov, Vladimir G. Bespalov, Mikhail V. Korsakov, Anton I. Ovsyannikov, Irina G. Popovic, Nikolai P. Napalkov and Lorenzo Tomatis	515
Singel-strand breaks in DNA of various organs of mice induced by administration of styrene S.A.S. Walles and I. Orsén	517
Investigation of absorption, metabolism and DNA binding of particle adsorbed PAH in the isolated perfused and ventilated rat lung Sam Törnquist, Lars Wiklund and Rune Toftgård	519
Genetic control of N-acetoxy-2-acetylaminofluorene (NA-AAF) induced unscheduled DNA synthesis and NA-AAF binding to DNA determined in mononuclear leukocytes of twins Ronald W. Pero, Carl Bryngelsson, Tomas Bryngelsson and Ake Nordén	521
Age and diet dependent binding of <sup>14</sup> C-dimethylnitrosamine meta- bolites to mouse liver chromatin Maria Klaude and Alexandra von der Decken	
Harra Kraude and Arexandra von der Decken	523
IN VIVO AND IN VITRO MODEL SYSTEMS OF CHEMICAL CARCINOGENESIS	
Metabolism of N-nitrosamines and effects of formaldehyde on DNA repair in cultured human tissues and cells Roland C. Grafström and Curtis C. Harris	527
Early changes in gene expression during hepatocarcinogenesis Snorri S. Thorgeirsson, Peter J. Wirth and Ritva P. Evarts	541
Mechanisms of initiation and promotion of carcinogenesis in mouse epidermis	
Stuart H. Yuspa	547

Metabolic activation of aromatic amines and the induction of liver, mammary gland and urinary bladder tumors in the rat Charles M. King, Ching Y. Wang, Mei-Sie Lee, Jimmie B. Vaught, Masao Hirose and Kenneth C. Morton	557
Comparisons of benzo( $\alpha$ )pyrene metabolism and DNA-binding between species and individuals: observations in rodent trachea and human endometrium David G. Kaufman, Marc J. Mass, Bonnie B. Furlong and B. Hugh Dorman	567
Mechanisms involved in multistage chemical carcinogenesis in mouse skin T.J. Slaga	577
NMRI NU/NU mouse skin fibroblasts: regain of arylhydrocarbon hydroxylase inducibility of transformed cell lines after a tumor phase Mariitta Laaksonen, Rauno Mäntyjärvi, Osmo Hänninen and Asta Rautiainen	587
Modulating effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on skin carcinogenesis initiated by 7,12-dimethylbenz(a)anthracene in CF-l swiss mice Pierre Lesca	589
Role of diethylstilbestrol (DES) quinone formation in hamster kidney tumor induction Joachim G. Liehr, Beverly B. DaGue and Annie M. Ballatore	591
In vitro cultivation of embryonic rat tongue cells and induction of GGT positive clones by benzo(a)pyrene: a good model system for oral carcinogenesis studies K.V. Kesava Rao, A.V. D'Souza and S.V. Bhide	593
Rabbit alveolar macrophage - mediated mutagenesis of polycyclic aromatic hydrocarbons in V79 chinese hamstercells Lennart Romert and Dag Jenssen	593
Inhibitory effects of some thiol compounds on the metabolic activation of dimethylnitrosamine (DMN) and dimethylhydrazine (DMH) in guinea-pig hepatocytes and enterocytes Stanislav Yanev, Gabrielle Hauber, Michael Schwenk and Herbert Remmer	599
Accumulation of carcinogens and drugs in cells as determined by fluorescence microscopy Erich Zeeck and Herbert Kowitz	601
Prediction of carcinogenic and mutagenic potencies using the PLS method Ulf Edlund, Sven Hellberg, Dan Johnels, Bo Nordén and Svante Wold	
	603

	XVI
Benzo(a)pyrene metabolism in human hair follicle cells: possible indicators for individual differences in susceptibility to chemical carcinogens Math W.A.C. Hukkelhoven, Lisette W.M. Vromans and Alphons J.M. Vermorken	605
Elucidation of the antineoplastic potency of vitamin C on benzo(a)pyrene induced tumors in rats George Kallistratos, Erhard Fasske, Andreas Donos, Vassiliki Kalfakakou-Vadalouka and Angelos Evangelou	609
Bronchiolar epithelial cell necrosis and selective impairment of pulmonary microsomal monooxygenases in mice by naphthalene and 1,1-dichloroethylene Theodore E. Gram, Klaas R. Krijgsheld, Samuel S. Tong, Edward G. Mimnaugh, Michael A. Trush and Michael C. Lowe	613
Effect of inducers of AHH on proliferation of mitogen-stimulated human lymphocytes. Benzanthracene-induced increase in proliferation of cells showing low response to mitogen and its toxicity in cells showing high response to mitogen Andrzej L. Pawlak, Krzysztof Wiktorowicz and Renata Mikstacka	615
Benzo(a)pyrene metabolizing enzymes and lymophocyte stimulation in patients with bronchial carcinoma Christel Bluhm and Edgar E. Ohnhaus	617
Studies on a nasal cavity carcinogen: metabolism and binding of phenacetin in the mucosa of the upper respiratory tract Eva Brittebo and Maria Ahlman	619
Metabolism and binding of chlorobenzene in the mucosa of the upper respiratory tract Ingvar Brandt and Eva Brittebo	621
The renal metabolism of a glutathione conjugate of the carcinogen hexachloro-1,3-butadiene: evidence for the formation of a mutagenic metabolite in the rat kidney Trevor Green, John A. Nash, Jenny Odum and Edwin F. Howard	623
Dose- and sex-related variation in the disposition and hepatic effects of cinnamyl anthranilate in the mouse John Caldwell, Andrew Anthony, Ian A. Cotgreave, Susan A. Sangster and J. David Sutton	625
Author index	627

### COMPARATIVE ASPECTS OF EXTRAHEPATIC AND HEPATIC DRUG METABOLISM AND CHEMICAL CARCINOGENESIS