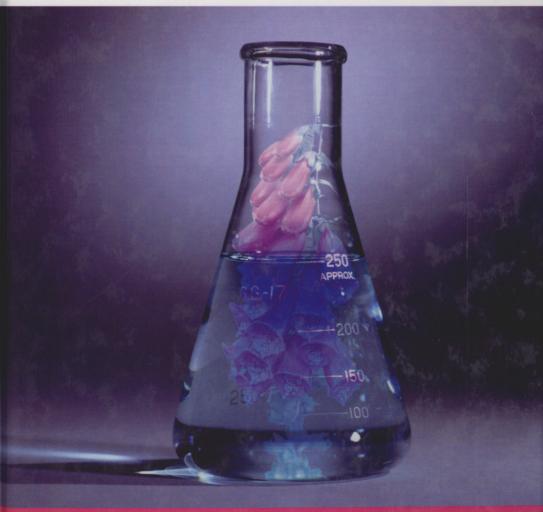
Fundamental TOXICOLOGY

Edited by John H Duffus and Howard G J Worth



RSCPublishing

299 W {

Fundamental Toxicology

Edited by

John H. Duffus

The Edinburgh Centre for Toxicology

Howard G. J. Worth

Healthcare Scientist Consultant

江苏工业学院图书馆 藏 书 章

ISBN 0-85404-614-3

A catalogue record for this book is available from the British Library

© The Royal Society of Chemistry 2006

All rights reserved

Apart from fair dealing for the purposes of research for non-commercial purposes or for private study, criticism or review, as permitted under the Copyright, Designs and Patents Act 1988 and the Copyright and Related Rights Regulations 2003, this publication may not be reproduced, stored or transmitted, in any form or by any means, without the prior permission in writing of The Royal Society of Chemistry, or in the case of reproduction in accordance with the terms of licences issued by the Copyright Licensing Agency in the UK, or in accordance with the terms of the licences issued by the appropriate Reproduction Rights Organization outside the UK. Enquiries concerning reproduction outside the terms stated here should be sent to The Royal Society of Chemistry at the address printed on this page.

Published by The Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge CB4 0WF, UK

Registered Charity Number 207890

For further information see our web site at www.rsc.org

Typeset by Macmillan India Ltd, Bangalore, India Printed by Biddles Ltd, King's Lynn, Norfolk, UK Fundamental Toxicology



Frontispiece Potentially toxic and dangerous chemicals are now part of our everyday life, both in our homes and in our places of work. (Photo: Courtesy of H.G.J. Worth, The King's Mill Centre for Health Care Services, Sutton-in-Ashfield)

Preface

When the first edition of *Fundamental Toxicology for Chemists* was published in 1996, we recognised the increasing awareness of safety and a growing consciousness of the need for safety standards. This had resulted in legislation concerned with safe practice in the work place, which was led by Europe and North America and other developed countries and which had spread to many other areas of the world.

In the United Kingdom the trend was spearheaded by the Health and Safety at Work Act in 1974, followed by legislation in 1978 concerned with safe practice of work in clinical laboratories and post mortem rooms, and then by regulations for the Control of Substances Hazardous to Health (COSHH). At the international level, the International Programme on Chemical Safety (IPCS), a joint activity of the World Health Organisation (WHO), the United Nations Environmental Programme (UNEP) and the International Labour Organisation (ILO) have published many valuable documents on chemical safety in conjunction with the Commission of the European Communities (CEC). This is merely one example of international collaboration. At present, the European Union is about to introduce a new regulatory framework in the form of the Registration Evaluation and Authorisation of Chemicals (REACH) proposals, which will cover all the constituent countries.

Much safety legislation and safe practice is concerned with the correct handling and use of chemicals. It is expected that chemists should be aware of the dangers of the chemicals that are used in their laboratories, and that there should be documentation and legislation to help this safety process. But the use of chemicals is not confined to the laboratory or the factory. Chemicals are used increasingly in domestic and non-technical environments, where their safe handling is no longer solely the concern of qualified chemists. For instance, consider the use of domestic cleaners, solvents and detergents, weed killers and pesticides and proprietary medicines. The question is asked, therefore, who is the person to whom the public might turn to seek help and advice in the safe handling of these chemicals? As like as not, the answer that comes back is, the chemist. It is not unreasonable that the chemist is seen as the person who can give help and advice on the handling of chemicals, on the toxic effects associated with them, and on how to deal with an incident if and when it occurs. However, the need is still not recognised in the curricula for the training of chemists, and indeed, apart from what they pick up indirectly during their educational progress, there is usually no formal training in toxicology. This makes the chemist very vulnerable as a result of being given new responsibilities without adequate training to handle them. Thus, this book was written originally with the chemist in mind.

vi

The above was the situation when we edited the first edition of *Fundamental Toxicology for Chemists*, but things have moved on. Even my daughter (HGJW) who appears in the Frontispiece of both editions is no longer a little girl! Legislation has increased. It has become more detailed and more complex, and even more widespread across the world. The public are better informed about toxic effects and their rights in relation to any consequential adverse effects. The scientific understanding of toxicology has increased and so, hopefully, has the knowledge of non-toxicologists, but it is unlikely to have kept up with the advances in toxicology. Thus, it has become necessary to produce a second edition of this book, not just for chemists, but for all those scientists who work with chemicals and now have to take the responsibility for any harm that may arise from their use. We are gratified that the Royal Society of Chemistry (RSC) has invited us to do this, and that it is again carried out under the auspices of the International Union of Pure and Applied Chemistry (IUPAC).

Every chapter has been reviewed and updated. As a result many have undergone a major restructuring, and some have been rewritten. Four new chapters have been added namely, 'Introduction to Toxicogenomics', 'Pathways and Behaviour of Chemicals in the Environment', 'Toxicology in the Clinical Laboratory' and 'Pharmaceutical Toxicology'. These have made the text a far more comprehensive guide to current toxicology than it was. The appendices include a 'Curriculum of Fundamental Toxicology for Chemists' and a 'Glossary of Terms used in Toxicology'. These were both in the previous edition, but have been revised. The glossary of terms is based on two IUPAC publications: J.H. Duffus, Glossary for Chemists of Terms Used in Toxicology (IUPAC Recommendations, 1993), Pure Appl. Chem., 1993, 65, 2003–2122; M. Nordberg, J.H. Duffus and D.M. Templeton, Glossary of Terms Used in Toxicokinetics (IUPAC Recommendations, 2004), Pure Appl. Chem., 2004, 76, 1033-1082. In addition, we have added a further appendix of commonly used abbreviations. This includes terms that are familiar to toxicologists such as lifetime average daily dose (LADD), for example, but are not so familiar to other scientists. It also includes the names of international bodies and pieces of legislation that are commonly abbreviated and may appear in other textbooks without definition.

Chemistry has had a poor press in recent decades partly because the public has the misconception that manmade chemicals are inherently bad and therefore toxic, while naturally occurring substances are inherently good and healthy. Nothing of course is further from the truth as may be illustrated by a survey of the use of animal and plant extracts over the centuries. It is well known that Cleopatra committed suicide by the administration of snake venom. Roman ladies distilled belladonna, which means beautiful woman, and used it as eye drops to make their pupils dilate. Belladonna is extracted from the plant known as deadly nightshade. Lucrezia Borgia made use of an extract from *Nux vomica* whose active ingredient is strychnine. This is to say nothing of Shakespeare's characters who took or administered an impressive range of animal and plant toxins. Hopefully, the explanation of the science of toxicology in this book will go some way to redressing the balance and putting manmade and natural chemicals into a proper perspective as parts of a total group of substances, and even micro-organisms, which must be considered as a whole in order to ensure their safe use.

Preface

Again, we thank IUPAC for their support of this project. In particular, we thank the committee of Division VII, Chemistry and Human Health, and the Subcommittee on Toxicology and Risk Assessment, for their encouragement and assistance. Finally, our thanks go to our team of internationally recognised authors without whose expertise and effort this book could not have been published.

John H. Duffus Howard G.J. Worth (Editors)

Contributors

- **A. Adisesh**, Health and Safety Laboratory, Harpur Hill, Buxton, Derbyshire SK17 9JN; e-mail: Anil.Adisesh@hsl.gov.uk.
- R. Agius, Director, Centre for Occupational and Environmental Health, The University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PL; e-mail: Raymond.Agius@manchester.ac.uk.
- **R.D.** Aldridge, Consultant Dermatologist, Department of Dermatology, Royal Infirmary NHS Trust, The Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9HA, Scotland.
- **H.R. Andersen**, Landesamt fur Natur und Umwelt des Landes Schleswig-Holstein, LGA SH 50, Brunswickerstr. 4, KIEL 24105, Germany.
- **D. Boverhof**, Biochemistry and Molecular Biology, Michigan State University, 223 Biochemistry Building, Wilson Road, East Lansing Michigan, MI 48824-1319, USA; e-mail: boverho5@msu.edu.
- **R.A.** Braithwaite, Regional Laboratory for Toxicology, Sandwell and West Birmingham NHS Trust, City Hospital, Birmingham B18 7QH.
- J. Burt, Biochemistry and Molecular Biology, Michigan State University, 223 Biochemistry Building, Wilson Road, East Lansing Michigan, MI 48824-1319, USA; e-mail: burtje@msu.edu.
- **J.H. Duffus**, The Edinburgh Centre for Toxicology, 43 Mansionhouse Road, Edinburgh EH9 2JD; e-mail: J.H. Duffus@blueyonder.co.uk.
- **J.S.L. Fowler**, Research and Liaison in Toxicology, 66 Meadow Road, Loughton IG10 4HX; e-mail: john.toni@btopenworld.com.
- **B. Heinzow**, Landesamt fur Natur und Umwelt des Landes Schleswig-Holstein, LGA SH 50, Brunswickerstr. 4, KIEL 24105, Germany; e-mail: birger.heinzow@lgash-ki. landsh.de.
- **R.F.M.** Herber, Tollenslaan 16, Bilthoven, NL-3723 DH, The Netherlands; e-mail: Rob@herber.com.
- M. Herrchen, Fraunhofer Institute of Molecular Biology and Applied Ecology, Schmallenberg D-57392, Germany; e-mail: Monika.Herrchen@ime.fraunhofer.de.
- **H.P.A. Illing**, PICS, Sherwood, 37 Brimstage Road, Heswall, Wirral CH80 1XE; e-mail: paul@sherwood37.demon.co.uk.
- **D. McGregor**, Toxicity Evaluation Consultants, 38 Shore Road, Aberdour Fife KY3 OTU, Scotland, UK; e-mail: mcgregortec@btinternet.com.

xxvi Contributors

A.L. Jones, Medical Director - National Poisons Information Service, Guy's and St. Thomas' Hospital Trust, Medical Toxicology Unit, Avonley Road, London SE14 5ER, England; e-mail: Alison.Jones@gstt.nhs.uk.

- **D.A.** Mckay, Department of Dermatology, Royal Infirmary NHS Trust, The Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9HA, Scotland.
- M.V. Park, 28 Coltbridge Terrrace, Edinburgh EH12 6AE, Scotland; e-mail: m.v.park@ntlworld.com.
- A.G. Renwick, Clinical Pharmacology Group, School of Medicine, University of Southampton, Biomedical Sciences Building, Bassett Crescent East, Southampton SO16 7PX; e-mail: A.G.Renwick@soton.ac.uk.
- **D.M. Templeton**, Department of Laboratory Medicine and Pathobiology, University of Toronto, Medical Sciences Building, 1 King's College Circle, Toronto, Ontario M5S 1A8, Canada; e-mail: doug.templeton@utoronto.ca.
- F.M. Sullivan, Consultant in Toxicology, Harrington House, 8 Harrington Road, Brighton BN1 6RE, England; e-mail: fsullivan@mistral.co.uk.
- **G. Wild**, Department of Immunology, Sheffield Teaching Hospitals, NHS Trust, Sheffield S5 7YT; e-mail: graeme.wild@sth.nhs.uk.
- M. Wilkinson, Biological Sciences (T8), Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, Scotland; e-mail: M.Wilkinson@hw.ac.uk.
- G. Winneke, Head of Department–Medical Psychology, Medizinisches Institut Fur Umwelthygiene, Heinrich-Heine-Universitat Dusseldorf, Auf'm Hennekamp 50, 40225 Dusseldorf, Germany; e-mail: gerhard.winneke@uniduesseldorf.de.
- **H.G.J. Worth**, 1 Park Court, Mansfield, Nottinghamshire NG18 2AX; e-mail: howard.worth@btopenworld.com.
- **T. Zacharewski**, Biochemistry and Molecular Biology, Michigan State University, 223 Biochemistry Building, Wilson Road, East Lansing Michigan, MI 48824-1319, USA; e-mail: tzachare@pilot.msu.edu.

Contents

Chapter 1		1
	John H. Duffus 1.1 Introduction	1
		1 3
	1.2.1 Skin (Dermal or Percutaneous) Absorption	4
	1.2.2 Inhalation	4 5
	1.2.3 Ingestion	
	1.3 Adverse Effects	6
	1.4 Chemical Interactions	7
	1.5 Tolerance and Resistance	8
	1.6 Toxicity Testing	8
	1.6.1 Dose–Response and	110
	Concentration–Response	8
	1.7 Epidemiology and Human Toxicology	11
	1.7.1 Cohort Study	11
	1.7.2 Retrospective Study	15
	1.7.3 Case Control Study	15
	1.7.4 Cross-Sectional Study (of Disease	
	Prevalence and Associations)	15
	1.7.5 Confounding	15
	Bibliography and Date of Date of State	16
84	4.4.1 The Inductive-Hypothetico Approach	
Chapter 2	Introduction to Toxicodynamics	17
	Robert F.M. Herber	
	2.1 Introduction	17
	2.2 Dose–Toxicity Relationships	18
	2.2.1 Dose–Effect Relationship	18
	2.2.2 Biological Effect Monitoring	21
	2.2.3 Dose–Response Relationship	21
	2.2.4 Acute and Chronic Effects	21
	2.3 Toxicity Testing and Health Risk	22
	Bibliography	22

X	Contents

Chapter 3		icokine		24
			Renwick	
	3.1	Introd	luction	24
	3.2	Absor	ption	27
		3.2.1	Rate of Absorption	28
		3.2.2	Extent of Absorption	29
	3.3	Distri	bution	30
		3.3.1	Rate of Distribution	30
		3.3.2	Extent of Distribution	31
	3.4	Elimi	nation	34
	3.5	Chron	nic Administration	37
	3.6	Satura	ation Kinetics	38
	3.7	Toxic	okinetics and Risk Assessment	40
	3.8	Concl	usions accombodal 1.1	41
	Bibl	liograph	1.2 Exposure to Potentially Toxic v	41
		eous) A	1.2.1 Skin (Dermal or Percutar	
Chapter 4			pretation doubledal 2.2.1	43
	John	n S.L. F		
	4.1		Adverse Effects noitou	43
		4.1.1	The Data Package [1] [Bolimon]	43
		4.1.2		43
		4.1.3	Use of Data to Assess Chemical Hazard	44
	4.2	Risk A	Analysis and Risk Management	45
		4.2.1	Contents of the 'Data Package' for	
			Risk Analysis	45
		4.2.2		
			May be Inadequate	45
		4.2.3	Decision Taking Without All the	
			Required Data	46
	4.3	Data 1	Retrieval bas sonolavors	46
		4.3.1	The Search for Information	47
	4.4		of Data ydgargoildia	48
		4.4.1	The Inductive-Hypothetico Approach	48
		4.4.2	Data Arising from the Study of	Chapte
			Chemical Toxicity	49
	4.5	Handl	ing Quantitative Data Using	.,
	110		tical Analysis	49
			The Null Hypothesis	49
			Generation of Data Relating to	17
		gide	Chemical Safety	50
		4.53	Presentation of Data	50
			Expression of Results as Tables, Graphs,	30
		11011	Figures and Statistics (Figure 4.1)	50

Contents	Xi
----------	----

	4.6	Evaluation of Experimental Data	52
		4.6.1 NOEL, ADI and TLV	52
		4.6.2 Extrapolation	52
		4.6.3 Exposure, Dose, Surface Area and Allometry	53
	4.7	Errors and Faults in Data Interpretation	53
		4.7.1 ADI or TLV are not Immutable Numbers	53
		4.7.2 False-Positive and False-Negative Results	54
		4.7.3 'Eyeballing' the Data	54
	4.8	Conclusion Consumption E.S.O.	54
	Bibl	liography present a softman a postal A A A a	55
		6.9 Conclusions pragass-Arand C. 3	
Chapter 5	Diel	k Assessment galanaoudal	56
Chapter 5		Paul A. Illing	50
	5.1	Introduction gravolmoM bas causous is a sequence.	56
		Definitions motstages Management	56
		Process of Risk Assessment	57
	5.4		57
	3.4	5.4.1 Sources of Information	57
		5.4.2 Types of Information	59
		5.4.3 Dose–Response, Dose–Effect, LD50	37
		and the 'No Observed (Observable)	
		Adverse Effect Level	59
		5.4.4 Hazard Characterisation	61
		5.4.5 Source–pathway–receptor	62
		5.4.6 Measurement and Modelling	62
		5.4.7 Human Exposure	64
		5.4.8 Environmental Exposure	66
		Risk Characterisation	68
	3.3	5.5.1 Humans	68
		5.5.2 Environmental Risk	70
	5.6		70
		liography	70
			70
Chapter 6	Ris	k Management	72
	H. I	Paul A. Illing	
	6.1	Introduction	72
	6.2	The Risk Evaluation and Management Process	72
	6.3	Risk Considerations	73
	6.4	Criteria for Risk Evaluations: Human Health	75
		6.4.1 Equity and Risk–Benefit	75
		6.4.2 Conventional Toxicity	
		(Non-Stochastic Effects)	76

		6.4.3	Stochastic Effects	79
		6.4.4	Major Accident Hazards	80
	6.5		a for Risk Evaluation: Environment	81
	6.6		ble Risk	84
	6.7	Criteri	a for Risk Evaluation: Further Comments	84
	6.8		Management	84
			Anticipated Exposure and Minor Accidents	84
			Product Safety	85
			Enforcement Management 8.4	86
		6.8.4	Major Accident Hazards	86
	6.9	Conclu	asions	86
	Bib	liography	er 5 Risk Assessment soitoniX no.V	86
Chapter 7	Evr	ocure o	nd Monitoring	00
Chapter 7			Templeton	88
	7.1		action amazaza A stata ha zezoona e e	0.0
			l Principles	88
			a for a Monitoring Programme	89
	7.5	7 3 1	Is Biological Monitoring a Useful	91
			Supplement to Ambient Monitoring?	0.1
			Is there Sufficient Information on the	91
			Handling of the Substance by the Body to	
			Justify Biological Monitoring?	91
			Is there a Reliable Analytical Method for	91
		0.01	Measuring the Chosen Parameter?	92
			Is the Measurement Interpretable?	92
			Are the Consequences of the Measurement	92
			Foreseeable?	92
	7.4		kers and Sensitivity Screening	93
	,		Biomarkers of Exposure to	93
			Non-Carcinogens	93
			Biomarkers of Exposure to Carcinogens	94
			Biomarkers of Susceptibility	95
	7.5		Considerations	96
		iography		97
		8		71
Charter	C	4. 75	6.1 Introduction	
Chapter 8				98
		glas Mc(
	8.1			98
	8.2		re of DNA (Deoxyribonucleic Acid)	98
	8.3	Types o	of Genetic Damage	101

xiii

	8.4	Repair of Damaged DNA	102
		8.4.1 Excision Repair	102
		8.4.2 Post-Replication Repair	103
		8.4.3 Base Replacement	103
			103
	8.5	Chromosomal Change	104
	8.6	Transmissible Human Genetic Damage	104
		Tests for Genetic Toxicity	106
		8.7.1 Test Categories	106
		8.7.2 Commonly Used Tests	107
		8.7.3 Data Assessment	107
	8.8	Conclusion	110
	Bibl	liography and the state of the	111
		Three and the West Street, Toxicity	
Chapter 9	Cor	cinogenicity	112
Chapter 9	Dou	eglas McGregor	112
	9.1		112
		Mechanisms of Carcinogenicity	113
	9.2	9.2.1 Genes	
		9.2.2 DNA Analysis	113 113
			113
		9.2.3 Hereditary and Nonhereditary Forms of Cancer	114
			114
		9.2.4 Genotoxic and Non-genotoxic	115
	0.2	Mechanisms	115
	9.3	Tests for Carcinogens	122
		9.5.1 The Standard Test	122
	0.4	9.3.2 Alternative Tests	123
	9.4	Epideimology	124
		Conclusion	125
	Bibl	liography	126
Chapter 10	In	troduction to Toxicogenomics	127
	Da	rrell Boverhof, Jeremy Burt and Timothy Zacharewsk	i
	10.	1 Introduction	127
	10.	2 Microarray Technology	127
		10.2.1 Array Platforms	128
		10.2.2 Sample Labeling and Hybridization	130
		10.2.3 Image Analysis	131
		10.2.4 Data Analysis and Interpretation	131
		10.2.5 Microarray Standards	132
		10.2.6 Microarrays in Toxicology	132

xiv	Contents

	10.3 Proteomics	133
	10.3.1 Mass Spectrometry-Based Proteomics	134
	10.3.2 Protein Microarrays	136
	10.3.3 Proteomics Standards	136
	10.4 Metabonomics Overview	137
	10.4.1 Applications and Approaches	137
	10.5 Conclusions	139
	Bibliography	139
Chapter 11	Reproductive Toxicity	142
107	Frank M. Sullivan	300
	11.1 Introduction	142
	11.2 Risk Assessment for Reproductive Toxicity	143
	11.3 Thresholds in Reproductive Toxicity	143
	11.4 Screening Tests in Animals for Reproductive	
	Toxicity Toxicity	143
	11.4.1 Drug Testing	144
	11.4.2 International Harmonisation of	91
	Drug-Testing Guidelines	144
	11.4.3 Safety Testing of Other Chemicals,	
	Namely Pesticides, Food Additives,	
	Industrial Chemicals	145
	11.4.4 Pesticide Testing	146
	11.4.5 Food Additive Testing	147
	11.4.6 Industrial Chemicals Testing	147
	11.5 Extrapolation of Results of Animal	92
	Studies to Humans	148
	11.6 The European Community Classification of	1.10
	Chemicals for Reproductive Toxicity	148
	11.7 The Seventh Amendment to EC Directive	4.40
	67/548/EEC 1992	149
	11.8 Classification of Chemicals as Toxic for	1.40
	Reproduction	149
	11.0.1 Effects of fitting of 1	149
	11.8.2 Developmental Toxicity	150
	11.9 Categorisation	150
	11.10 Lactation	150
	11.11 Testing Requirements under the Dangerous	
	Substances Directive	151
	11.12 Downstream Consequences Relating to the	719 202
	Classification of Chemicals (CMR Substances)	151
	Bibliography	152

Chapter 12	Immunology and Immunotoxicology 154				
	Graen				
	12.1	Introdu	ction	154	
	12.2	Innate 1	nate Immunity		
			ve Immunity	155	
	12.4	Humor	al Immunity company and the last	155	
	12.5	Cell-M	ediated Immunity	156	
	12.6		d Type Hypersensitivity	156	
	12.7		ement moonmond 1.3.1	157	
	12.8	Hypers	ensitivity of Hymol S. J. J. J.	157	
		12.8.1	Type I: IgE-Mediated (Immediate)		
			Hypersensitivity	157	
		12.8.2	Type II: Antibody-Mediated		
			Hypersensitivity	158	
		12.8.3	Type III: Immune Complex-Mediated		
			Hypersensitivity	158	
		12.8.4	31		
			Hypersensitivity	158	
	12.9	Immun	odeficiency	158	
	12.10	Autoi	mmunity Alexander Property	159	
	12.11	Transp	plantation	159	
	12.12	Vaccin	nation and a samuel and the same	160	
	12.13	Immu	notoxicology	160	
	Biblic	ography		161	
Chapter 13	3 Skin Toxicology			162	
	David		Tay and Roger D. Aldridge		
	13.1			162	
	13.2	Skin A	natomy of the Anatomy of the grant	162	
	13.3	Permea	ation Median to a main and on Market	164	
	13.4	Potency	15.3.1 Covalent Bouding	165	
			Toxicology	165	
	13.6	Dermat	15.3.3 Thiot Group Catit	165	
	13.7		Accumulation, Metabolism and		
		Transpo		166	
	13.8		cal Carcinogenesis	167	
	13.9		olet Radiation	168	
	13.10	Enzyr	15.3.8 DNA Damage am	168	
	13.11		isomes applied A P. F. F.	169	
		Concl		169	
	Biblio	ography		170	