IEH report on

PERINATAL DEVELOPMENTAL NEUROTOXICITY

From contributions by Jennifer Court, Vincenzo Cuomo, Per Eriksson, Elaine Perry, Andrew Pickles, David Ray, Patricia Rodier, Mark Stanton, Eric Taylor and Faraneh Varga-Khadem
The Institute for Environment and Health was established by the Medical Research Council at the University of Leicester in 1993. The Institute is partly funded by the Department of the Environment, the Department of Health and other Government Departments and Agencies by way of specific research and consultancy contracts.

This report incorporates the output of a workshop held in March 1995, and has been prepared by the Institute for Environment and Health under the auspices of the Medical Research Council’s Neurosciences Approach to Human Health initiative. The workshop was chaired by Trevor Robbins from the Department of Experimental Psychology at the University of Cambridge. The Institute gratefully acknowledges the contribution of all those who attended the workshop and provided material for inclusion in the Report, but assumes no endorsement from these scientists for the conclusions and recommendations contained here.

The views expressed here do not necessarily represent those of any Government Department or Agency.

From contributions by Jennifer Court, Vincenzo Cuomo, Per Eriksson, Elaine Perry, Andrew Pickles, David Ray, Patricia Rodier, Mark Stanton, Eric Taylor and Faraneh Vargha-Khadem

Edited by Barbara MacGibbon and David Ray

Published by the Institute for Environment and Health

© Institute for Environment and Health

Printed by Page Bros

ISBN 1 899110 06 2

Institute for Environment and Health
University of Leicester
94 Regent Road
Leicester LE1 7DD
Preface

This report, which is based on a workshop hosted by the Institute for Environment and Health in Leicester in March 1995, has been prepared under the auspices of the Medical Research Council’s Neurosciences Approach to Human Health (NAHH) initiative. The NAHH initiative aims to encourage high quality innovative research that meets at least one of the following criteria: ‘(i) uses novel approaches that may lead to an understanding of causation, or to clinical advances in the medium-term in under-researched areas; (ii) exploits opportunities to apply molecular and cellular biology to the understanding of neural mechanisms commonly affected by disease; or (iii) bridges psychological and clinical disciplines within the framework of neurobiology’.

The main text of the report is based on written contributions prepared by a number of authors in advance of the workshop; these contributions have been amended based on the discussions during the workshop.

The report presents an evaluation of the nature and significance of the developmental neurotoxicity of environmental and pharmaceutical agents in the perinatal period and recommends a general strategy for the development of future research.
LIST OF PARTICIPANTS

IEH WORKSHOP ON PERINATAL DEVELOPMENTAL NEUROTOXICITY

LEICESTER, UK, 15 & 16 MARCH, 1995

Members

Professor P Blain, Department of Environmental/Occupational Medicine, University of Newcastle upon Tyne, Framlington Place, Newcastle

Dr W Blakemore, Department of Clinical Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge

Dr D Bristow, Department of Biological Sciences, University of Manchester, G38 Stopford Building, Oxford Road, Manchester

Dr M R Carratu, Institute of Pharmacology, Medical School, University of Bari, Italy, 70124 Bari, Italy

Professor J Cavanagh, Department of Neurology, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London

Dr R Clayton, Institute of Cell, Animal & Population, University of Edinburgh, West Mains Road, Edinburgh

Dr J Court, MRC Neurochemical Pathology Unit, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne

Dr V Cuomo, Institute of Pharmacology, Medical School, University of Bari, Italy, 70124 Bari, Italy
PARTICIPANTS

Professor M Cutler, Department of Biological Sciences, Glasgow Caledonian University, Southbrae Campus, Southbrae Drive, Glasgow

Dr J Edwardson, MRC Neurochemical Pathology Unit, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne

Dr P Eriksson, Uppsala University, Department of Zoophysiology, Norbyvagen 18a, 75236 Uppsala, Sweden

Dr M Feenstra, Netherlands Institute for Brain Research, Miebergdreef 33, 1105 A2 Amsterdam, The Netherlands

Professor J Golding, Department of Child Health, University of Bristol, Respiratory Research Group, Royal Hospital for Sick Children, St Michael’s Hill, Bristol

Dr R Goodman, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London

Professor D Graham, Neuropathology, Southern General Hospital, Glasgow

Dr S Jaggers, BIBRA, Woodmansterne Road, Carshalton, Surrey

Dr M Jepson, MRC Head Office, 20 Park Crescent, London

Dr M Johnson, MRC Cognitive Development Unit, 4 Taviton Street, London

Dr I Kitchen, School of Biological Sciences, University of Surrey, Guildford, Surrey

Professor R Kumar, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London

Dr A E Lock, Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire

Dr T Marrs, Department of Health, Room 511A Skipton House, 80 London Road, London

Professor C Marsden, Department of Physiology and Pharmacology, University of Nottingham Medical School, Queen’s Medical Centre, Nottingham

Dr B Mohammed, MRC Toxicology Unit, Neurotoxicology Department, University of Leicester, Hodgkin Building Lancaster Road, Leicester
Dr D Murphy, Psychological Medicine, Institute of Psychiatry, 113 Denmark Hill, London

Dr E Perry, MRC Neurochemical Pathology Unit, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne

Dr A Pickles, MRC Child Psychiatry Unit, Institute of Psychiatry, De Crispigny Park, Denmark Hill, London

Dr D Ray, MRC Toxicology Unit, University of Leicester, Hodgkin Building Lancaster Road, Leicester

Dr T Robbins, University of Cambridge, Department of Experimental Psychology, Downing Street, Cambridge (Chairman)

Dr P Rodier, University of Rochester, Medical Centre, Strong Memorial Hospital, 601 Elmwood Avenue, Box 668 Rochester, New York 14642, USA

Professor Sir Michael Rutter, MRC Child Psychiatry Unit, Institute of Psychiatry, De Crispigny Park, Denmark Hill, London

Dr B Sahakian, Department of Psychiatry, Level 4, University of Cambridge, Addenbrooke’s Hospital, Cambridge

Dr A Sahgal, MRC Neurochemical Pathology Unit, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne

Dr G Sarna, MRC Head Office, 20 Park Crescent, London

Dr L Scott, CDE, Porton Down, Salisbury, Wiltshire

Dr M Stanton, USEPA, Health Effects Research Laboratory, Research Triangle Park, NC 27711, USA

Dr A Stollery, 8 Woodland Road, University of Bristol, Bristol

Professor E Taylor, MRC Child Psychiatry Unit, Institute of Psychiatry, De Crispigny Park, London

Dr C Tuckett, Department of the Environment, 43 Marsham Street, London
PARTICIPANTS

Dr K van den Berg2, TNO Toxicology, Nutrition and Food Research, Department of Neurotoxicology, PO Box 5815, 2280 HV Rijswijk, The Netherlands

Dr F Vargha-Khadem2, Institute of Child Health, 30 Guildford Street, London

Dr P Winn, School of Psychology, University of St Andrews, Western Lane, St Andrews, Fife, Scotland

Secretariat

Dr P Harrison, Programme Manager, IEH, Leicester
Dr J Havercroft2, MRC Head Office, London
Dr L Shuker2, Head of Publications and Information Unit, IEH, Leicester
Professor L Smith, Director, IEH, Leicester

Technical assistance

Mrs P Forster2, IEH, Leicester
Miss S Howe2, IEH, Leicester

1Participated on first day of workshop only, unless otherwise specified
2Participated on both days of workshop
3Unable to attend
Much of our present knowledge of the adverse effects of chemical agents on human brain development relates to actions at early stages of development, during gestation. However, developmental neuroscience clearly indicates that many potentially sensitive processes (such as cell migration and apoptosis, or synaptic formation and trimming) occur during the post-natal period of brain maturation in both humans and animals. There is also experimental evidence from studies with rats and mice that post-natal exposure to certain environmental and pharmaceutical agents, acting either directly or indirectly on the nervous system, can lead to persisting changes in adult neurochemistry and behaviour. Often these effects are more subtle than classical teratogenic effects, and are seen at dose levels producing no acute toxicity.

There are however a number of problems in extrapolating these experimental studies to man. The first relates to study design. A number of investigations have shown that there are clear developmental time windows of vulnerability to toxic agents, yet most studies involve potentially insensitive conception to weaning exposure schedules. The second is that those researchers who have demonstrated adverse developmental effects in experimental animals have as yet used endpoints (such as open field behaviour) that are either too crude to yield information about mechanisms or are too limited in scope (such as changes in a single receptor type). Better understanding of the mechanisms involved is needed for prediction of risks to humans. In addition, clinical studies have been hampered by the difficulty of defining dose and period of exposure retrospectively, and of eliminating confounding variables.

Before further progress can be made, a more integrated and multidisciplinary approach is needed, drawing on a wider range of applied and fundamental scientific expertise. Standardised behavioural and other indices capable of being used in both animals and humans are available from the general neurosciences, and should be applied in toxicologically appropriate study designs. In clinical research a prospective cohort study of a defined population, such as neonates given analgesics, would be of value.