This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organization or the World Health Organization.

## **Environmental Health Criteria 237**

# PRINCIPLES FOR EVALUATING HEALTH RISKS IN CHILDREN ASSOCIATED WITH EXPOSURE TO CHEMICALS

First drafts prepared by Dr Germaine Buck Louis, Bethesda, USA; Dr Terri Damstra, Research Triangle Park, USA; Dr Fernando Díaz-Barriga, San Luis Potosi, Mexico; Dr Elaine Faustman, Washington, USA; Dr Ulla Hass, Soborg, Denmark; Dr Robert Kavlock, Research Triangle Park, USA; Dr Carole Kimmel, Washington, USA; Dr Gary Kimmel, Silver Spring, USA; Dr Kannan Krishnan, Montreal, Canada; Dr Ulrike Luderer, Irvine, USA; and Dr Linda Sheldon, Research Triangle Park, USA

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.



The International Programme on Chemical Safety (IPCS), established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO) and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing-in-Publication Data

Principles for evaluating health risks in children associated with exposure to chemicals (Environmental health criteria; 237)

"First drafts prepared by Dr Germaine Buck Louis ... [et al.]."

1.Environmental health. 2.Risk assessment. 3.Child. 4.Organic chemicals - adverse effects. 5.Inorganic chemicals - adverse effects. 6.Environmental exposure. I.Louis, Germaine Buck. II.World Health Organization. III.Inter-Organization Programme for the Sound Management of Chemicals. IV.Series.

ISBN 92 4 157237 X ISBN 978 92 4 157237 8 ISSN 0250-863X (NLM classification: WA 30.5)

©World Health Organization 2006

All rights reserved. Publications of the World Health Organization can be obtained from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int). Requests for permission to reproduce or translate WHO publications — whether for sale or for noncommercial distribution — should be addressed to WHO Press, at the above address (fax: +41 22 791 4806; e-mail: permissions@who.int).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

The named authors alone are responsible for the views expressed in this publication. This document was technically and linguistically edited by Marla Sheffer, Ottawa,

Canada, and printed by Wissenchaftliche Verlagsgesellschaft mbH, Stuttgart, Germany.

#### **CONTENTS**

## ENVIRONMENTAL HEALTH CRITERIA ON PRINCIPLES FOR EVALUATING HEALTH RISKS IN CHILDREN ASSOCIATED WITH EXPOSURE TO CHEMICALS

PKI	EAMB	LE	X
PRI	EFACE	3	xvii
AC	RONY	MS AND ABBREVIATIONS	xix
1.		MARY, CONCLUSIONS, AND DMMENDATIONS	1
	1.1 1.2	Summary Conclusions and recommendations	1 4
2.	INTR	ODUCTION AND BACKGROUND	7
	2.1 2.2 2.3 2.4 2.5 2.6 2.7	Introduction Purpose and scope of document Global burden of disease in children Major environmental threats to children 2.4.1 Economic and nutritional factors 2.4.2 Social, cultural, demographic, and lifestyle factors 2.4.3 Chemical hazards Intrinsic factors The significance of a developmental stage approach Summary and conclusions	7 9 12 14 15 16 17 19 20 21
3.		QUE BIOLOGICAL CHARACTERISTICS OF DREN	22
	3.1 3.2 3.3	General physical growth of children 3.1.1 Body weight and height 3.1.2 Organ weights/volumes 3.1.3 Skin Anatomical and functional characteristics Physiological characteristics	22 22 23 25 25 26
		, .	

		3.3.1	Breathing	rate	26	
		3.3.2	Cardiac ou	utput	26	
		3.3.3	Blood flow to organs			
		3.3.4	Body composition			
		3.3.5	Tissue cor	nposition	29	
		3.3.6	Bone grov	wth and composition	29	
	3.4	Metal	olic charac	eteristics	29	
	3.5	Toxicokinetics			31	
	3.5.1 Absorption, distribution, metabolism, an					
			eliminatio		31	
		3.5.2	Physiological changes in mothers and their			
			influence of	on toxicokinetics	33	
			3.5.2.1 P	regnancy	33	
			3.5.2.2 L	actation and breast milk	35	
		3.5.3	Dose to ta	rget	36	
	3.6	Normal development			39	
		3.6.1 Basic principles of normal development				
		3.6.2	Nervous s	ystem	40	
		3.6.3	Reproduct	tive system	42	
		3.6.4	Endocrine	system	44	
			3.6.4.1 H	Hypothalamic-pituitary axis	44	
			3.6.4.2 T	hyroid gland	46	
				Adrenal glands	47	
			3.6.4.4	onads	48	
			3.6.4.5 S	Somatotropin (growth hormone),		
			c	alcium homeostasis, and bone		
				evelopment	48	
			3.6.4.6 P	ancreas	48	
		3.6.5	Cardiovas	cular system	49	
		3.6.6	Immune sy	ystem	49	
		3.6.7	Respirator	ry system	50	
		3.6.8	Kidney		52	
	3.7	Sumn	mmary and conclusions			
4.	DEVELOPMENTAL STAGE-SPECIFIC					
	SUSCEPTIBILITIES AND OUTCOMES IN CHILDREN					
	4.1	4.1 Introduction				
	4.2	Morta	ortality, growth restriction, and birth defects			
			2.1 Mortality			
		4.2.2	Growth re	striction	63	
		4.2.3	Birth defects (structural malformations)		64	

		4.2.3.1	Etiology	66
		4.2.3.2	Functional developmental toxicity	67
4.3		fic organ		68
	4.3.1	Nervous	s system	68
4.3		4.3.1.1	Periods of susceptibility and	
			consequences of exposures	69
		4.3.1.2	Specific examples	72
	4.3.2	Reprodu	uctive system	78
			Periods of susceptibility	79
		4.3.2.2	Consequences of exposures	80
	4.3.3	Endocri	ne system	85
		4.3.3.1	Periods of susceptibility	85
			Consequences of exposures	92
	4.3.4	Cardiov	ascular system	95
		4.3.4.1	Periods of susceptibility	96
		4.3.4.2	Consequences of exposures	96
	4.3.5	Immune	esystem	97
		4.3.5.1	Periods of susceptibility	98
		4.3.5.2	Consequences of exposures	101
	4.3.6	Respira	tory system	105
		4.3.6.1	Periods of susceptibility	105
		4.3.6.2	Consequences of exposures	106
	4.3.7	Kidney		113
		4.3.7.1	Periods of susceptibility	113
		4.3.7.2	Consequences of exposures	114
	Cance	er		115
	4.4.1	Childho	od cancers that may have	
		environ	mental causes	116
			Lymphoid tissues	116
		4.4.1.2		118
			Thyroid	118
		4.4.1.4	Brain and nervous system	119
			Other organ sites	119
	4.4.2	Adult cancers related to childhood		
		exposures		120
		4.4.2.1	Brain and nervous system	120
		4.4.2.2	Thyroid	121
		4.4.2.3	Female breast	122
			Female reproductive tract	122
			Integument	122
		4.4.2.6	Other organ sites	123

		4.4.3	Chemic	al exposures of special concern	123	
	4.5	Sumn	nary and	conclusions	126	
5.	EXP	OSURE	E ASSES	SMENT OF CHILDREN	129	
	5.1	Introd	luction		129	
	EXPOSURE ASSESSMENT OF CHILDREN	129				
	5.3	Meth	ods for co	onducting exposure assessments	133	
		5.3.1	Direct n	nethods	133	
		5.3.2	Biomar	kers of exposure	136	
		5.3.3	Modelli	ing	137	
	5.4			teristics of children that affect		
	5.5				144	
					144	
		5.5.2	Pathway	*	145	
					145	
					150	
					152	
					153	
					154	
			5.5.2.6	-		
					155	
		5.5.3			156	
					157	
					157	
					157	
					158	
					159	
		5.5.4				
	<b>5</b> 6	a .			161	
	5.6	_	•			
		5.6.1			162	
					162	
					162	
			5.6.1.3		162	
			5611		162	
		5.60			163	
					163 164	
		3.0.3		-	164	
			5.0.5.1	Chiorpythos	104	

				Smelter areas	165		
				Malarious areas	165		
				tive exposure	165		
	5.7	Sumn	nary and	conclusions	166		
6.	METI	HODO	LOGIES	TO ASSESS HEALTH			
	OUT	COME	S IN CH	ILDREN	168		
	6.1	Introd	Introduction				
				ological approaches for children's			
			health studies		168		
				Epidemiological methods	171		
				Comparison of study designs	171		
				Descriptive designs	176		
				Analytic designs	178		
				Unique methodological			
				considerations	180		
		6.1.2	Method	ological approaches for animal			
			studies		181		
			6.1.2.1	Developmental stage susceptibility,			
				dosing periods, and assessment of			
				effects	184		
			6.1.2.2	Dosing of fetuses and pups	190		
	6.2	Grow	th and de	velopment	190		
		6.2.1	Human		190		
			6.2.1.1	Puberty	194		
			6.2.1.2	Birth defects	195		
		6.2.2	Animal	studies	195		
			6.2.2.1	Body weight and postnatal growth	195		
				Pre-, peri-, and postnatal death	196		
			6.2.2.3				
				developmental landmarks	196		
				Birth defects and malformations	198		
	6.3	Reproductive development and function			198		
			Human		198		
		6.3.2	Animal		202		
			6.3.2.1	Malformations of reproductive			
				organs	202		
			6.3.2.2	2	203		
				Nipple/areola retention	204		
			6.3.2.4	Sexual maturation and puberty	2.04		

			6.3.2.5		204		
			6.3.2.6	Histopathology of reproductive			
				organs	206		
			6.3.2.7	Sperm quality and estrous cyclicity	207		
	6.4	Neuro	Neurological and behavioural effects				
		6.4.1	Human s	tudies	207		
		6.4.2	Animal s	studies	208		
			6.4.2.1	Motor activity	208		
			6.4.2.2	Motor and sensory functions	209		
			6.4.2.3	Learning and memory	209		
			6.4.2.4	Evaluation of effects	210		
	6.5	Cance	r		211		
		6.5.1	Human s	tudies	211		
		6.5.2	Animal s	studies	212		
	6.6	Immu	Immune system effects				
		6.6.1	Human s	tudies	212		
		6.6.2	Animal s	studies	213		
	6.7	Respi	Respiratory system effects				
		6.7.1	Human s	tudies	213		
		6.7.2	Animal s	studies	213		
	6.8	,					
		skin/n	nusculoskeletal, and metabolic/endocrine				
		systen	n effects		214		
		6.8.1	Human s	tudies	214		
		6.8.2	Animal s	studies	214		
	6.9	Summ	ary and c	onclusions	214		
7.	IMPLICATIONS AND STRATEGIES FOR RISK						
	ASSESSMENT FOR CHILDREN 21						
	7.1	Introd	luction				
	7.2	Proble	plem formulation				
	7.3				220 221		
		7.3.1	End-poir	nts and critical periods of exposure	223		
			Human s		224		
		7.3.3		ce of animal studies for assessing	22-		
			notential	hazards to children	225		

# i束,完整报告链接和二维码如下: