
CONTENTS

ENVIRONMENTAL HEALTH CRITERIA FOR DERMAL ABSORPTION

PREAMBLE	x
ACRONYMS AND ABBREVIATIONS	xvii
1. SUMMARY	1
2. INTRODUCTION AND DEFINITIONS	6
2.1 Scope of the document	6
2.2 Definition of dermal absorption	8
2.3 Factors influencing dermal absorption	8
3. SKIN STRUCTURE AND FUNCTION	10
3.1 Functions of the skin	10
3.1.1 Barrier function	10
3.1.2 Temperature control	11
3.1.3 Defence and repair	11
3.2 Skin structure	12
3.2.1 Epidermis	12
3.2.2 Dermis	16
3.2.3 Skin appendages	16
3.3 The transport of chemicals through the skin	17
3.4 Variability in skin permeability	17
3.4.1 Species	17
3.4.2 Age, sex, and race	18
3.4.3 Anatomical site	19
3.4.4 Skin condition	19
3.4.5 Temperature and blood flow rate	19
3.4.6 Hydration	20
3.5 Reservoir effects	20

4.	SKIN TRANSPORT MECHANISMS AND THEORETICAL CONCEPTS	23
4.1	Transport through the skin	23
4.2	Theoretical aspects of diffusion	23
4.3	Physicochemical factors affecting skin permeation	26
4.3.1	Physical state	27
4.3.2	Molecular size/molecular weight	27
4.3.3	Maximum flux	28
4.3.4	Ionization	28
4.3.5	Binding properties	29
4.4	Concepts of finite and infinite dose	29
5.	METABOLISM IN THE SKIN	32
5.1	The drug-metabolizing systems of the skin	33
5.2	Methodology for evaluating skin metabolism in vitro systems	35
5.3	Effects of skin metabolism	35
5.4	Importance of metabolism for percutaneous absorption	36
6.	IN VITRO TESTS FOR DERMAL ABSORPTION	38
6.1	Test guidelines	38
6.2	Principles of the standard in vitro tests using skin samples	39
6.2.1	Test chambers	39
6.2.1.1	Static diffusion cells	40
6.2.1.2	Flow-through cells	40
6.2.1.3	Comparison of different in vitro cell systems	42
6.2.2	Finite/infinite dosing	43
6.2.3	Skin preparations	44
6.2.3.1	Choice of skin	44
6.2.3.2	Preparation of tissue samples	45
6.2.3.3	Checking of barrier integrity	46
6.2.4	Application of test substance	47
6.2.4.1	Test substance	47
6.2.4.2	Vehicle	48
6.2.4.3	Receptor fluid	48
6.2.4.4	Application dose levels	50

6.2.5	Duration of exposure and sampling time	50
6.2.6	Evaluation of the results	50
6.2.6.1	Dermal absorption results after finite dosing	51
6.2.6.2	Dermal absorption results after infinite dosing	52
6.3	Other in vitro methods	52
6.3.1	Artificial skin	52
6.3.2	Tape-stripping technique in vitro	52
6.4	Examination of skin reservoir characteristics	53
6.5	Experimental factors affecting dermal absorption in vitro	54
6.5.1	Species differences	54
6.5.2	Temperature	55
6.5.3	Occlusion	56
6.5.4	Thickness of skin	56
6.5.5	Further observations on application vehicle effects	58
7.	IN VIVO TESTS FOR DERMAL ABSORPTION	60
7.1	Laboratory animal studies	60
7.1.1	Test guidelines for laboratory animal studies	61
7.1.2	Principles of the standard in vivo tests	61
7.1.2.1	Preparation of the application site	62
7.1.2.2	Dose levels	62
7.1.2.3	Application of the test substance to the skin	62
7.1.2.4	Duration of exposure	63
7.1.2.5	Sacrifice and time of termination	63
7.1.2.6	Evaluation of the results	64
7.2	Studies with human volunteers	65
7.2.1	Assessment using plasma, excreta, and breath analysis	66
7.2.1.1	Methodology	66
7.2.1.2	Examples of in vivo human volunteer studies	66
7.2.1.3	Biomonitoring of occupational exposure	67
7.2.2	Cutaneous microdialysis	68
7.2.3	Tape stripping	70

7.3	Other methods	73
7.3.1	Whole-body autoradiography	73
7.3.2	Skin biopsy	73
7.4	Factors affecting dermal absorption in vivo	74
7.4.1	Species, strain, and sex	74
7.4.2	Age	75
7.4.3	Anatomical site	75
7.4.4	Type of application and vehicle	77
7.4.5	Temperature and humidity conditions	78
8.	COMPARATIVE STUDIES	79
8.1	Comparison between in vitro and in vivo skin absorption results	79
8.2	Inter- and intralaboratory variation in in vitro percutaneous absorption methodology	84
9.	DATA COLLECTIONS	86
9.1	Data sets from homologous or closely related molecules	86
9.2	Flynn data set	87
9.3	Expanded permeability coefficient data sets	88
9.4	EDETOX database	88
9.5	Maximum flux databases	89
10.	ESTIMATION/PREDICTION OF DERMAL PENETRATION	90
10.1	QSAR analysis	91
10.1.1	Prerequisites for QSPeR analysis	91
10.1.2	Historical overview	92
10.1.2.1	QSPeRs for skin permeability prior to the 1990s	92
10.1.2.2	The Flynn (1990) data set and subsequent analyses	93
10.1.2.3	Other data sets	97
10.1.3	Other approaches to QSPeR	97
10.1.4	Variability of data and its relevance for QSPeRs	98
10.1.5	Statistical analysis (linear vs non-linear) methods	98

10.1.6	Selection of chemicals for further tests on dermal penetration	98
10.1.7	Applicability domain for QSPeR	99
10.1.8	Maximum fluxes	99
10.1.9	Rules as an alternative to QSPeRs	100
10.2	Mathematical modelling	100
10.3	Mathematical pharmacokinetic models of percutaneous penetration	103
11.	USE OF DERMAL PENETRATION STUDIES IN RISK ASSESSMENT	105
11.1	Decision-making process for setting dermal absorption values	106
11.1.1	Default values	107
11.1.2	Measured values	108
11.1.3	Values from mathematical skin permeation models (e.g. QSARs/QSPeRs)	110
11.2	Use of relative absorption values versus flux (and their derived permeability coefficients)	110
11.3	Other topics related to risk assessment	111
12.	CONTROVERSIAL TOPICS IN THE ASSESSMENT OF DERMAL ABSORPTION	112
12.1	QSARs/QSPeRs	112
12.2	Reduction of intralaboratory/interlaboratory variation	112
12.3	Consequences of reservoir effect for risk assessment	113
12.4	Relevance of percutaneous measurements to data required by risk assessors: finite and infinite exposures	114
12.5	Single- versus multiple-exposure regimes	114
12.6	Barrier integrity test for skin barrier function of human skin in skin penetration tests	115
12.7	Dermal absorption in susceptible populations	115
12.8	Skin notation	117
12.8.1	Skin notation criteria in different countries	118
12.8.2	Quantitative approaches	119
12.8.3	New approaches	120
12.9	Dermal absorption of nanoparticles	121

13. CONCLUSIONS AND RECOMMENDATIONS	124
REFERENCES	127
APPENDIX 1: GUIDELINES AND PROTOCOLS	163
APPENDIX 2: PAST AND PRESENT INITIATIVES ON EXCHANGE OF INFORMATION AND HARMONIZATION OF METHODOLOGY ON DERMAL ABSORPTION	170
RESUME	186
RESUMEN	192