

# IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 244

## Principles and methods to assess the risk of immunotoxicity associated with exposure to nanomaterials



IOMC INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS  
A cooperative agreement among FAO, ILO, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD



World Health  
Organization

# IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

IOMC INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS  
A cooperative agreement among FAO, ILO, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

## **Environmental Health Criteria 244**

# PRINCIPLES AND METHODS TO ASSESS THE RISK OF IMMUNOTOXICITY ASSOCIATED WITH EXPOSURE TO NANOMATERIALS

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.



**World Health  
Organization**

Principles and methods to assess the risk of immunotoxicity associated with exposure to nanomaterials (Environmental health criteria 244)

ISBN 978 92 4 157244 6

ISSN 0250-863X

© World Health Organization 2019

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization.

**Suggested citation.** Principles and methods to assess the risk of immunotoxicity associated with exposure to nanomaterials (Environmental Health Criteria: n. 244). Geneva: World Health Organization; 2019. Licence: [CC BY-NC-SA 3.0 IGO](https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

**Cataloguing-in-Publication (CIP) data.** CIP data are available at <http://apps.who.int/iris>.

**Sales, rights and licensing.** To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

**Third-party materials.** If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

**General disclaimers.** 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 WHO 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 and dashed 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 WHO 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 expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

This document was produced with the financial assistance of the European Union. The views expressed herein can in no way be taken to reflect the official opinion of the European Union.

Printed in Switzerland

# CONTENTS

PREFACE	xi
ACKNOWLEDGEMENTS	xiii
ABBREVIATIONS	xviii
EXECUTIVE SUMMARY	xxiv
1. INTRODUCTION	1
1.1 Scope of the document	1
1.2 Engineered nanomaterials and nanotechnologies	1
1.3 Immunotoxicity testing	7
References: Chapter 1	9
2. TYPES OF NANOPARTICLES	14
2.1 Categorization of nanoparticles	16
2.1.1 Carbon-based nanomaterials	16
2.1.2 Metal-based nanomaterials	19
2.1.3 Organic-based and other nanomaterials	21
2.1.4 Composite nanomaterials	23
2.2 Next ENM generations	24
2.3 Life cycle of nanomaterials	24
2.4 Functionalization	26
2.5 Interaction of nanoparticles with physiological fluids	27
References: Chapter 2	28
3. HUMAN EXPOSURE	33
3.1 Exposure to nanomaterials	33
3.1.1 Occupational exposure	34
3.1.2 General population exposure through environment	35
3.1.3 Consumer exposure	35
3.2 Route of exposure	36
3.2.1 Inhalation exposure	36
3.2.2 Oral exposure	37

3.2.3	Dermal exposure	38
3.2.4	Other routes	39
3.3	Epidemiology and health surveillance	39
3.4	Toxicokinetics	46
3.4.1	Introduction	46
3.4.2	Methods to evaluate toxicokinetics of nanomaterials	47
3.4.3	Absorption, distribution, metabolism and excretion	50
3.4.4	Specific considerations for toxicokinetic studies on nanoparticles	55
	References: Chapter 3	56
4.	MECHANISMS OF IMMUNOTOXICITY	64
4.1	General principles of toxicity of nanomaterials	64
4.1.1	Role of physicochemical material properties	64
4.1.2	Direct cytotoxic effects of nanomaterials	67
4.1.3	Altered cellular signalling by nanomaterials	67
4.1.4	Role of oxidative stress for nanotoxicity	68
4.2	Nanoparticle interactions with the immune system	69
4.2.1	Innate immune system	70
4.2.2	Cellular and soluble mediators of inflammation	74
4.2.3	Inflammasome activation by nanomaterials	77
4.3	Nanomaterials and the adaptive immune system	79
4.4	Immunosuppression versus immune activation	81
4.5	Immunogenicity of engineered nanomaterials	82
4.6	Nanoparticles as adjuvants	83
4.7	Immunologically susceptible populations	85
4.8	The role of the biomolecule corona	85
4.9	The microbiome and the immune system	89
4.10	Immunotoxicity depending on route of exposure	92
4.10.1	Dermal exposure to engineered nanomaterials	92
4.10.2	Impact of nanomaterials on the respiratory system	100
4.10.3	Exposure to nanomaterials via the gastrointestinal tract	121
4.11	Human studies of nanomaterials	139

4.12	Other exposure routes relevant for occupational settings	141
4.13	Placental exposure	142
	References: Chapter 4	145
5.	CONTROLLED EXPOSURE METHODS AND DOSIMETRY	176
5.1	Dispersion methods	176
5.1.1	Aerosol generation	176
5.1.2	Liquid suspension	181
5.1.3	Characterization of nanosuspension	183
5.2	Exposure methods	185
5.2.1	In vivo exposure methods for inhalation studies	185
5.2.2	Dermal exposure methods	188
5.2.3	Oral exposure methods	188
5.2.4	Other exposure methods	189
5.2.5	In vitro exposure methods	190
5.3	Metrics of dose	191
5.4	Dosimetry	192
	References: Chapter 5	195
6.	HAZARD ASSESSMENT	199
6.1	Introduction	199
6.2	Test material considerations	203
6.2.1	Endotoxin contamination	203
6.2.2	Storage and handling of nanomaterials in laboratories	205
6.2.3	Endotoxin detection methods	205
6.2.4	Recommendations or suggested modifications for testing endotoxin contamination	209
6.3	Preparation of nanomaterials for exposure and characterization	209
6.4	Animal species, routes of exposure, and exposure duration and levels	212
6.4.1	In vivo: animal species	212
6.4.2	Routes of exposure	212
6.4.3	Duration and levels of exposure	215

6.4.4	Multiple exposure versus single exposure	216
6.5	In vitro cell types, exposure methods, duration and levels	216
6.6	Routinely used cell types of the respiratory system	218
6.6.1	Cells of the innate immune system	218
6.6.2	Specific cell types of the respiratory system: cells of the adaptive immune system	220
6.6.3	Specific cell types of the respiratory system: co-culture systems	221
6.6.4	Ex vivo precision-cut lung slice method to investigate nanomaterial-induced tissue responses	223
6.7	Pre-testing considerations and methods applicable to inhalation route (respiratory system)	224
6.7.1	In vivo pre-testing considerations	224
6.7.2	In vivo testing methods applicable to inhalation route (respiratory system)	228
6.7.3	In vitro testing methods applicable to inhalation route (respiratory system)	235
6.7.4	Testing considerations and methods applicable to dermal route (skin exposure)	240
6.7.5	In vitro/ex vivo and synthetic skin models	242
6.7.6	Skin cell cultures	243
6.7.7	Skin test methods for immunotoxicity	243
6.8	Testing considerations and methods applicable to oral route	252
6.9	Systemic exposure and translocation of nanomaterials into the bloodstream	255
6.10	Conclusions	256
	References: Chapter 6	257
7.	APPROACHES FOR RISK ASSESSMENT	277
7.1	Introduction	277
7.1.1	Hazard identification	279
7.1.2	Dose–response relationship	280
7.1.3	Exposure assessment	282
7.1.4	Risk characterization	282
7.1.5	Major issues with applying the existing HHRA paradigm to nanomaterials	283

7.1.6	Conclusions: application of conventional risk assessment approach to nanomaterials	293
7.2	Recent initiatives developing risk assessment approaches for nanomaterials	294
7.2.1	Introduction	294
7.2.2	Risk assessment approach by SCENIHR	296
7.2.3	Summary of risk assessment approaches developed in the recent European Union FP7 projects	299
7.2.4	Read-across approaches for identifying the risk of nanomaterials	302
7.3	Nanomaterial immunotoxicity risk assessment	304
7.3.1	Summary of existing immunotoxicity risk assessment approaches for chemicals and pharmaceuticals	304
7.3.2	Levels of evidence for concluding on immune system toxicity	307
7.3.3	Nanomaterial immunotoxicity risk assessment	308
7.4	New risk assessment approaches for nanomaterials and links with immunotoxic substances: conclusions	311
	References: Chapter 7	312
8.	FUTURE RESEARCH	326
8.1	Emerging toxicology paradigm	326
8.2	Global molecular screening to identify perturbed toxicity pathways, biological functions and processes	327
8.3	Mode of action and adverse outcome pathways	330

预览已结束，完整报告链接和二维码如下：

[https://www.yunbaogao.cn/report/index/report?reportId=5\\_24696](https://www.yunbaogao.cn/report/index/report?reportId=5_24696)

