Approaches for establishing human no-effect levels for engineered nanomaterials?#

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ENRHES

Engineered Nanoparticles: Review of Health and Environmental Safety project

http://nmi.jrc.ec.europa.eu/project/ENRHES.htm

- to perform a comprehensive and critical scientific review on four types of nanomaterials:
  - ▪ Fullerenes ▪ Carbon nanotubes ▪ Metal ▪ Metal oxide

WP 3 – Risk Assessment Analysis (JRC)

- effects and exposure assessment and basic risk assessments to the extent the database allows
- to draw substance specific and general conclusions in relation to knowledge gaps in data and methodology

Human No-Effect Level - Methodology

- DNEL (Derived No-Effect Level)/DMEL (Derived Minimal Effect Level) following REACH Guidance on "Information Requirements and Chemicals Safety Assessment"

http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm?time=1252482386

→ for substances > 10t/y (chemical safety assessment)

→ Risk is controlled: DNEL > exposure

- **Comparison with other methodologies:**
  - NEDO-project (AIST: Japanese Institute of Advanced Industrial Science and Technology): CNT, TiO_2, Fullerenes http://www.aist-riss.jp/main/?ml_lang=en
  - OEL for MWCNT Baytubes®; Pauluhn 2010; Reg Toxicol Pharmacol
  - NIOSH 2005: REL for ultrafine TiO_2 http://www.cdc.gov/niosh/review/public/Tio2/pdfs/TIO2Draft.pdf

Criteria for establishing Human No-Effect Levels

- Exposure route
- Key study (relevance, reliability, NM characterisation)
- Toxicokinetics
- Nature and severity of effect
  - Threshold or non-threshold mechanism
  - Local - systemic effects
- Dose descriptor
- Modification to the starting point
- Assessment factors

Modification and assessment factors

Modification to the starting point

- Differences in bioavailability
- Route to route extrapolation
- Differences in experimental and human exposure conditions
- Correction for respiratory volume

- 6/8h*6.7/10 m^3 = factor ~2

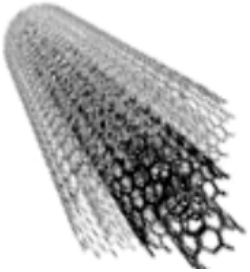
Table R. 8-6 Default assessment factors

Assessment factor – accounting for differences in:		Default value systemic effects	Default value local effects
Interspecies	- correction for differences in metabolic rate per body weight	AS[a, b]	–
	- remaining differences	2.5	1[f] 2.5[g]
Intraspecies	- worker	5	5
	- general population	10[c]	10[c]
Exposure			
	- dose-response, incl. LOAEL/NAEL extrapolation and severity of effect		
Quality of whole database	- issues related to completeness and consistency of the available data	1[d]	1[d]
	- issues related to reliability of the alternative data	1[e]	1[e]

Chemical specific assessment factors (CSAF) always to be given preference over default assumptions

a AS = factor for allometric scaling (see Table R. 8-3) ;
b Caution should be taken when the starting point is an inhalation or diet study
c Not always covering for very young children; see text for deviations from default
d See text for deviations from default
e Special consideration needed on a case-by-case basis
f for effects on skin, eye and GI tract via simple destruction of membranes
g for effects on skin, eye and GI tract via local metabolism; for effects on respiratory tract
h for effects on respiratory tract.

Inhalation toxicity studies



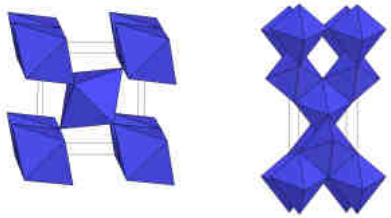
•MWCNT

2 Subchronic Inhalation Studies (OECD 413)

Baytubes® : NOAEC: **0.1 mg/m^3** (Pauluhn 2010a)

[Including post-exposure observation period up to 6 months]

Nanocyl: LO(A)EC: **0.1 mg/m^3**(Ma-Hock et al., 2009)



•Nano-TiO_2

Subchronic inhalation study (Bermudez et al., 2004)

NOAEC: **0.5 mg/m^3** (minimal effects at 2 mg/m^3)

(21 nm; anatase/rutile 80/20, [Including post-exposure observation period up to 52 weeks]

Chronic inhalation study (Heinrich et al., 1995)

10 mg/m^3: increased mortality and lung tumours in rats

Effects: Inflammation; overload at high doses

no systemic effects → Suggests threshold mechanism → DNEL

Human no effect levels: TiO_2

Approach	REACH	NEDO	NIOSH (2005)
Exposure duration	Sub-chronic	Sub-chronic	chronic
N(L)OAEC (dose descriptor)	0.5 mg/m^3	2 mg/m^3	(10 mg/m^3)
Correction for exposure time/ activity (6h/8h*6.7/10 m^3)	0.25 mg/	Lung deposition: F: 0.85	Extrapolation of tissue doses in rats to human equivalent doses; reduction of working lifetime risk for lung cancer < 1/1000
Interspecies differences (no allometric scaling)	1.5	1	
Intraspecies variation worker	5	1	
Duration: sub-chronic → chronic	2	2	
OAF (overall assessment factor)	**15** (1.5*5*2)*2	**1.7** (2 * 0.85)	**REL: 1.5 mg/m^3** (Micron size) **0.1 mg/m^3** (ultra fine)
Indicative Human No-effect level (INEL)	**17 µg/m^3**	**1.2 mg/m^3** **18 µg/kg/day**	

Human no effect levels: MWCNT

Approach	REACH	OEL (Pauluhn 2010)	NEDO
Substance	Baytubes®	Baytubes®	A Company
Exposure duration	Sub-chronic (90 d + 6 m)		Sub-acute (4w)
N(L)OAEC	0.1 mg/m^3	0.1 mg/m^3	0.37 mg/m^3
Modification to starting point (6h/8h*6.7/10 m^3)	0.05 mg/m^3	deposited dose: **1** (Ventilation and pulmonary deposition);	Lung deposition: 0.85
Interspecies differences	2.5	Humans more AM volume but longer clearance half life: 1.7 ~ **2**	1
Intraspecies variation worker	5	1	1
Duration	2	1	2
OAF (overall assessment factor)	**25** (2.5*5*2)*2	**2**	**1.7**
INEL	**2 µg/m^3**	**OEL: 50 µg/m^3**	**210 µg/m^3** **3 µg/kg/day**

Exposure to CNTs at workplace - Inhalation

- **0.7 µg/m³** (ablation facility), **53 µg/m³** (HiPCo process), SWCNT
- 64 and 93 µg/m³ (weighing and mixing with solvent), 1094 µg/m³ (wet saw) (Maynard et al., 2004)
- **430 µg/m³** and **40 µg/m³** (MWCNT, blending before and after exposure control); 194 and 173 fibers/ml (<5 µm) (Han et al. 2008)
- Baytubes: **< 1 µg/m³**
- Nanocyl **0.25 µg/m³** (R&D offices) and **1.45 µg/m³** (packaging)

Suggested ELs

$INEL_{chronic}$: **1 (2) µg/m³**

OEL Baytubes: **50 µg/m³**

DNEL Nanocyl: **2.5 µg/m³**

Conclusions

- Application of default assessment factors usually lead to higher assessment factors and lower human no-effect levels
- Other approaches base the interspecies differences basically on different deposition fractions in the lung

  lung deposition ≈ modification to starting point
- Remaining interspecies differences – reduced to <2.5 (1)?

  (animal exposure conditions might over estimate human risk – always?)
- Metrics?
- REACH Implementation Projects on Nanomaterials (RIP-oN) aim at developing advise on how the guidance documents (Information Requirements and Chemical Safety Assessment) could be updated
- Current database is very limited – no generalisations possible

Joint Research Centre (JRC)

Robust science for policy making

Thank you for your attention

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