DERIVATION OF HEALTH EFFECT FACTORS FOR NANOPARTICLES TO BE USED IN LCIA

with some notes on fate factors | Dr. H.E. Buist

innovation for life

Introduction

- Toxicological Risk Assessor of department of Risk Assessment of Products in Development (RAPID)
- at TNO, the Netherlands Organization for applied scientific research, a not-for-profit company

- INDUSTRY

- DEFENSE, SAFETY & SECURITY

- ENERGY

- URBANISATION

- HEALTHY LIVING

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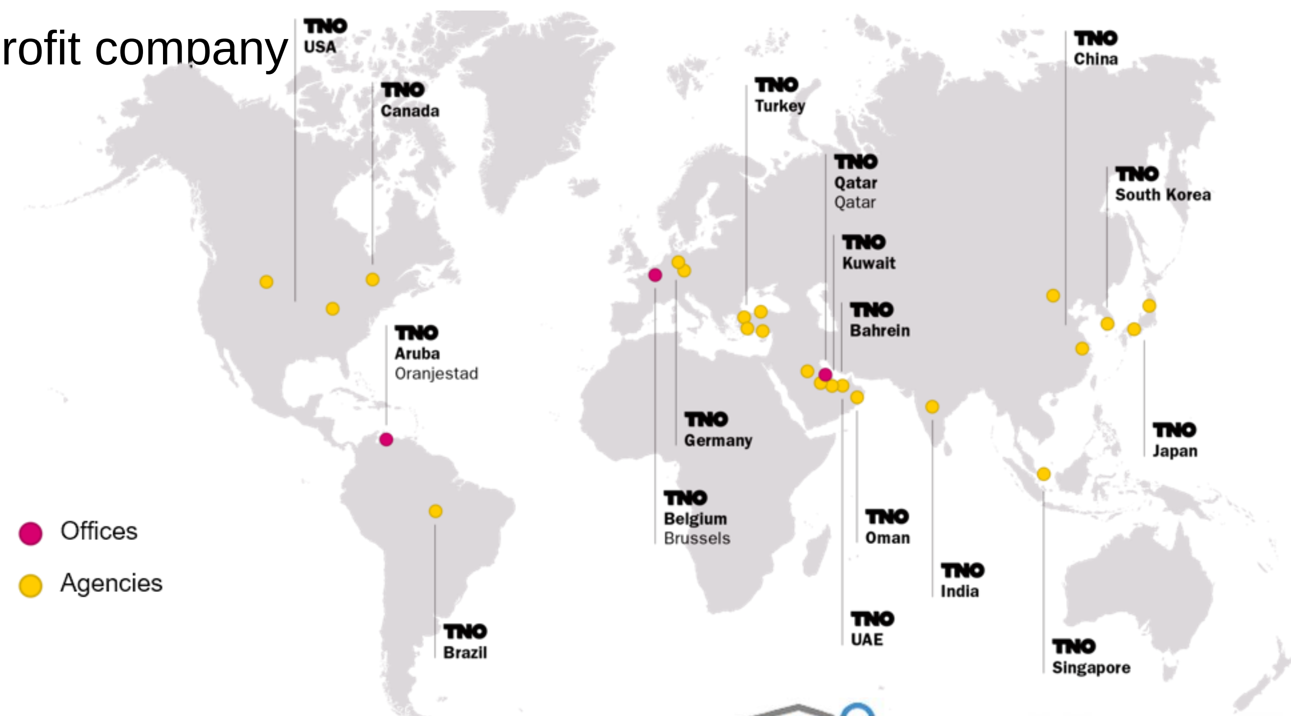


Introduction

- Toxicological Risk Assessor of department of Risk Assessment of Products in Development (RAPID)
- at TNO Innovation for Life, a not-for-profit Research Organization in Applied Sciences

- Presented work was executed with international partners in four different projects, co-funded by the EU:

  Licara (LIfe Cycle Approach and human Risk Assessment)

  NanoSolutions (Safety classification of nanomaterials)

  Adaptiwall (Adaptive Wall panel development)

  NanoFASE (Environmental fate of nanomaterials)

This presentation

- Central issue: Providing building blocks for the calculation of Health Characterisation Factors for nanoparticles in UseTox

Health Characterisation Factor = Health Effect Factor x Exposure Factor x Fate Factor

$$HCF = HEF \times XF \times FF$$

only respiratory route

- Focus: Main challenges encountered:

1. Nanospecific dose metrics
2. Intake (= inhaled dose) versus retained dose
3. Converting midpoints into endpoints
4. Nanofate

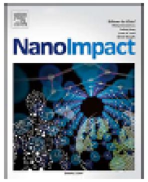
and some unpublished data

NanoImpact 7 (2017) 41–53

Contents lists available at ScienceDirect

NanoImpact

journal homepage: www.elsevier.com/locate/nanoimpact



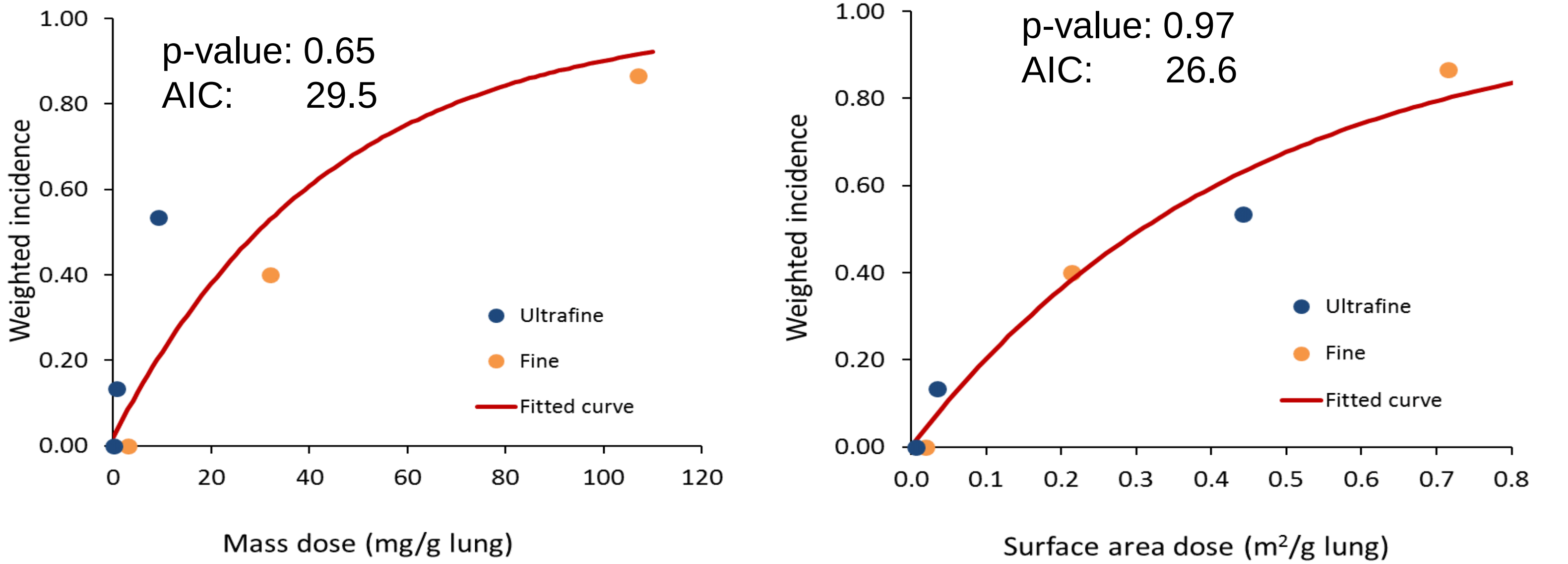
Derivation of health effect factors for nanoparticles to be used in LCIA

H.E. Buist[a,*], R. Hischier[b], J. Westerhout[a], D.H. Brouwer[c]

Issue 1 – dose metric

- UseTox uses mass based doses
- Relevant dose metric for nanoparticles often surface based

Incidence of alveolar hyperplasia in rats exposed to micro- or nanosized TiO_2
(Data provided by Ed Bermudez)

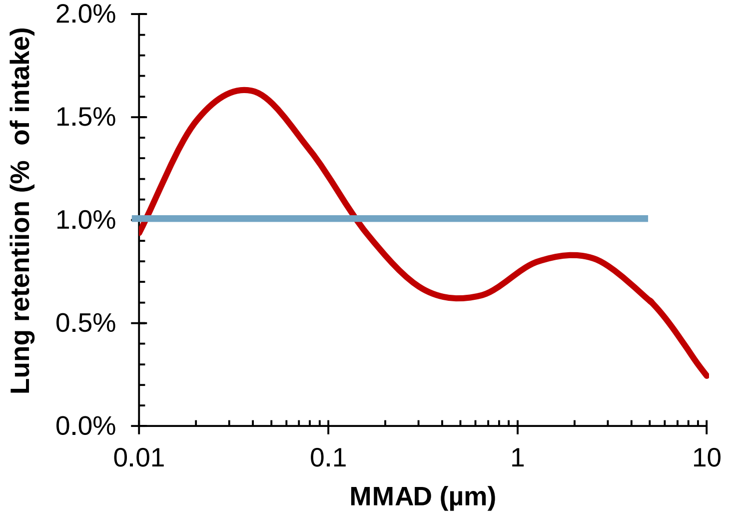


Solution:

- Normalise mass based health effect factors to 1 m^2/g
- Users of UseTox to multiply CF with surface area of specific nanoparticles concerned

Issue 2 – Intake vs retained dose

- UseTox applies intake calculated from air concentrations
- Health effects of inhaled nanoparticles are local in nature, depending on the particles retained in lungs
- Retention depends on size distribution air-borne particles and human breathing parameters



Relation between airborne particle size, retention and intake (calculated with MPPD model version 2.1) for continuously exposed general population

~~Back calculate retained dose to mass intake using MPPD model, size plus GSD of airborne particles and human breathing frequency and tidal volume~~

Solution:

For particle sizes of 0.01 to 5 µm:

Human retention factor: 0.010 (1.0%)

Issue 3 – midpoint to endpoint

- HEF from animal study in cases/kg intake (midpoint)
- Endpoint: DALYs = Disability Adjusted Life Years = Life years lost due to premature mortality plus years of productive life lost due to disability
- Translation of cases to DALYs needed

Solution:

- Use DALYs published by WHO
- Match symptoms in study used to derive HEF to symptoms of a disease in DALY list
- Acquire incidence/prevalence data from Institute of Health Metrics Evaluation
- Divide DALYs associated with the disease by its incidence/prevalence

Example:

Rat:
alveolar hypertrophy, focal fibrosis, chronic inflamma-tion

↔

COPD:
Chronic inflammation
small airway fibrosis

→

77,000,000 DALYs
329,000,000 patients
0.23 DALYs/case

Issue 4 – fate factor for nanoparticles

- Fate of nanoparticles is not covered by USEtox

Solution developed by Tom Ligthart and Bas Henzing:

- Use SimpleBox4Nano (SB4N) to derive size-dependent Fate Factors
- Modify compartments in SB4N to USEtox dimensions. E.g. ***Regional*** becomes ***Urban***
- Set environmental parameters in SB4N, as wind speed et cetera, to USEtox values
- Feed values of rate constants from SB4N into USEtox
- USEtox uses these rate constants to calculate Fate Factors and provides Human Intake Fractions (= XF x FF)

Carcinogenic HEFs for nanoparticles and some bulk chemicals

Nanoparticle/ bulk chemical	cancer cases/kg_{intake}
2,3,7,8-TCDD (dioxin, most potent carcinogen)	4.9E+04
MWCNT D (30,000 x 10^{12} f/kg)	2.0E+04
MWCNT B (1,600 x 10^{12} f/kg)	1.1E+03
Aflatoxin	3.8E+02
Chrysene (a PAH)	7.3E-01
MWCNT – Baytubes (259 m^2/g)	4.7E-01
N-Nitrosodiethanolamine (a nitrosamine)	3.6E-01
Carbon black (230 m^2/g)	2.7E-01
Chloroethene (vinyl chloride)	1.9E-01
TiO_2 (48 m^2/g)	1.6E-01
Carbaryl (insecticide)	8.1E-02
Benzene (often used reference compound)	1.5E-02

Acknowledgements

<u>Fellow authors:</u>
Joost Westerhout, Roland Hischier (EMPA), Derek Brouwer (University of the Witwatersrand)

<u>Providers of data, methods or advice</u>:
Amy VanderZanden (IHME; incidence/prevalence data), Bas Henzing (TNO, Fate model), Ed Bermudez (The Hamner Institutes for Health Sciences; TiO_2), Jack Harkema (Michigan State University; carbon black), Otto Creutzenberg (Fraunhofer ITEM; amorphous silica), Owen Price (Applied Research Associates, Inc.; MPPD model), Tom Ligthart (TNO, Fate model)

<u>LCIA discussions in EU projects Licara, Nanosolutions and Adaptiwall:</u>
Alejandro Vílchez (LEITAT), David Meyer (US EPA), Eelco Kuijpers, Elisabeth Keijzer, Esther Zondervan, Ewa Zukowska (Acciona), Mara Hauck, Maria Blázquez (INKOA), Rinke Klein Entink, Sieto Bosgra, Socorro Vázquez-Campos (LEITAT), Tobias Walser (Swiss Federal Office of Public Health), Wouter Fransman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MAIN STEPS DERIV[illegible] HUMAN HEALTH EFFECT FACTORS NAN[illegible]TICLES (1)

Inhalation only

Step 1: Description hazard profile based on substance specific hazard data

Step 2: Selection of relevant animal studies with respect to exposure route (respiratory/oral/dermal), duration (chronic) and type of effect (carcinogenic/non-carcinogenic)

Step 3: Decide on relevant dose metric (e.g. substance quantity: mass, surface area, number; nature of dose: intake, deposited dose, retained dose)

Step 4: Dose-response modelling using USEPA BMDS software to determine lifelong ED_{50} and extrapolation to human equivalent dose

Step 5: Convert ED_{50} unit to mass intake (expressed in kg)

Examples:

For surface dose: divide by surface area/mass of airborne particle

For deposited/retained dose: ?

MAIN STEPS DERIVATION HUMAN HEALTH EFFECT FACTORS NANOPARTICLES (2)

Step 6: Calculate human health effect factor: $\frac{0.5}{ED_{50}}$ cases/kg_{intake}

Step 7: Convert effect factor from cases to DALYs, based on WHO DALYs for non-infectious diseases

Uncertainty and variability

- Distribution estimated for each parameter based on SD's, GSD's or minimum and maximum
- Monte Carlo simulation to estimate overall uncertainty and variability

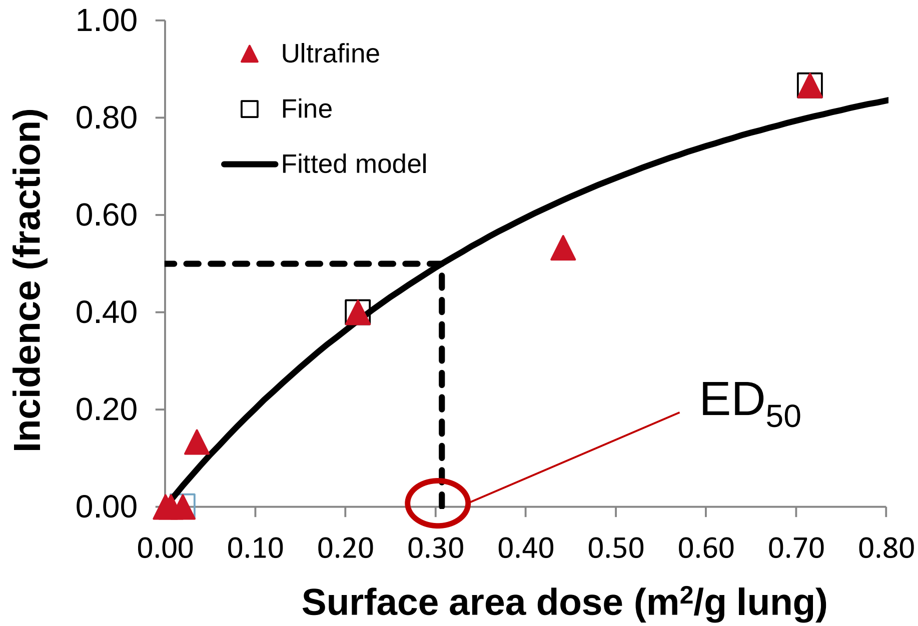
Example: Non-carcinogenic effects nanoTiO_2 (1)

Steps 1 - 4:

Source: Bermudez et al. (2002, 2004)

Effect: Alveolar Epithelial Cell Hypertrophy in rats

ED_{50} in rat: c. 0.31 m^2 retained/g lung



Extrapolation to human equivalent dose:

ED_{50} (m^2/g lung) x lung weight rat (g) / Lung surface rat (m^2) x Lung surface human (m^2) =

0.31 x 1.5 / 0.405 x 102.2 = 117 m^2 retained end of life/lungs

Example: Non-carcinogenic effects nanoTiO_2 (2)

Steps	Parameter	Calculation	Value
1-4	ED_{50} - human (m^2 retained end of life/lungs)		117
5	SA airborne particles (m^2/kg) (normalisation!)		1000
	ED_{50} - human (kg retained end of life/ lungs/m^2/g)	= 117 / 1000	0.117
	Retention factor		0.013
	ED_{50} - human (kg **intake**/ lungs/m^2/g)	= 0.117 x 1 / 0.013	9.0
6	Effect factor (cases /kg_{intake}/m^2/g)	= 0.5 / 9.0	0.056
7	DALYs COPD (2010)		76,731,358
	Prevalence COPD (2010) (cases)		328,943,524
	DALYs/case	= 76,731,35 / 328,943,52	0.23
	Effect factor (DALYs /kg_{intake}/m^2/g)	= 0.056 x 0.23	0.013