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Dosimetrische Extrapolation von Ergebnissen aus Rattenstudien zur Ableitung von Expositions-Standards

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UNIVERSITY of ROCHESTER MEDICAL CENTER

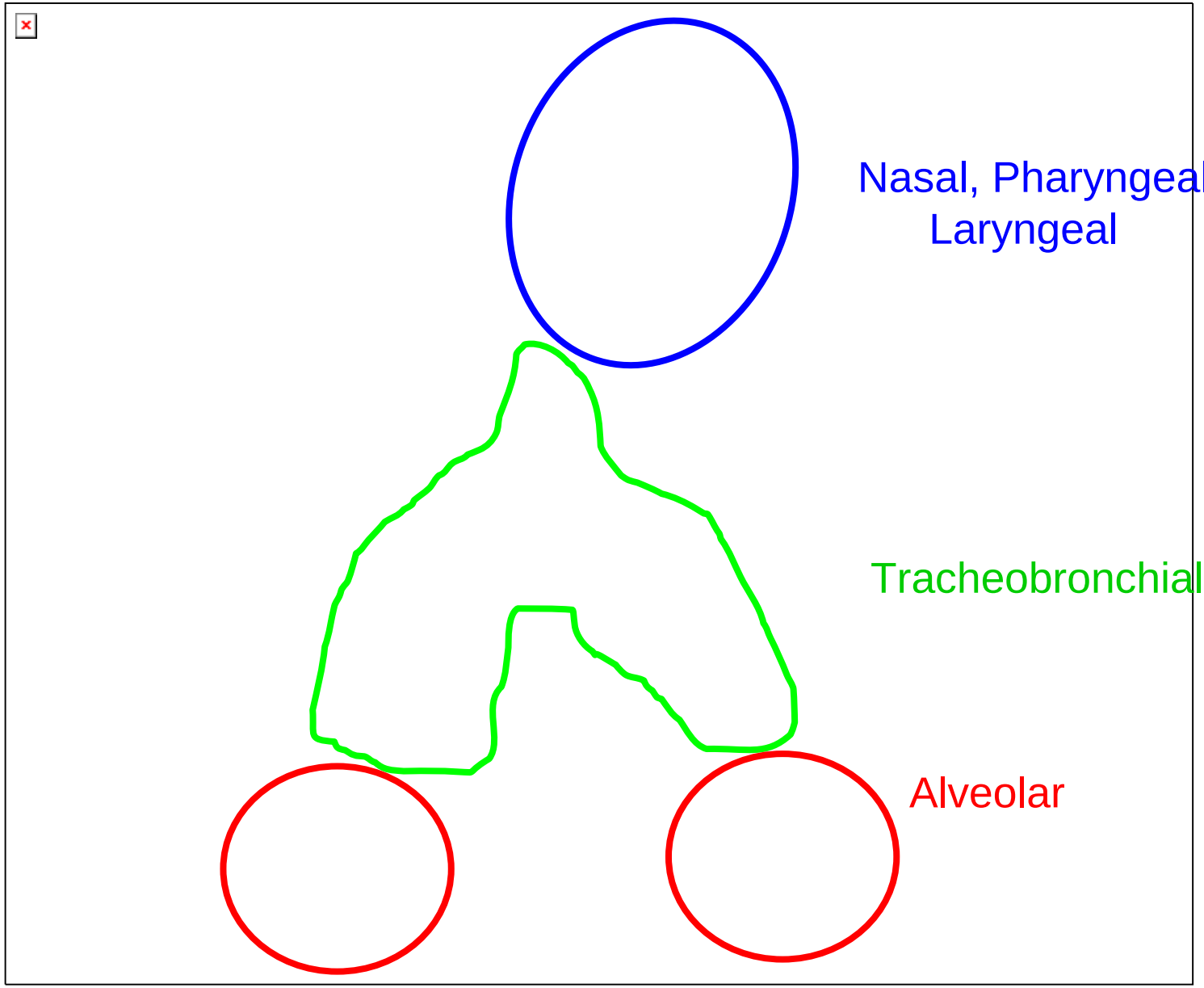
Übersicht:

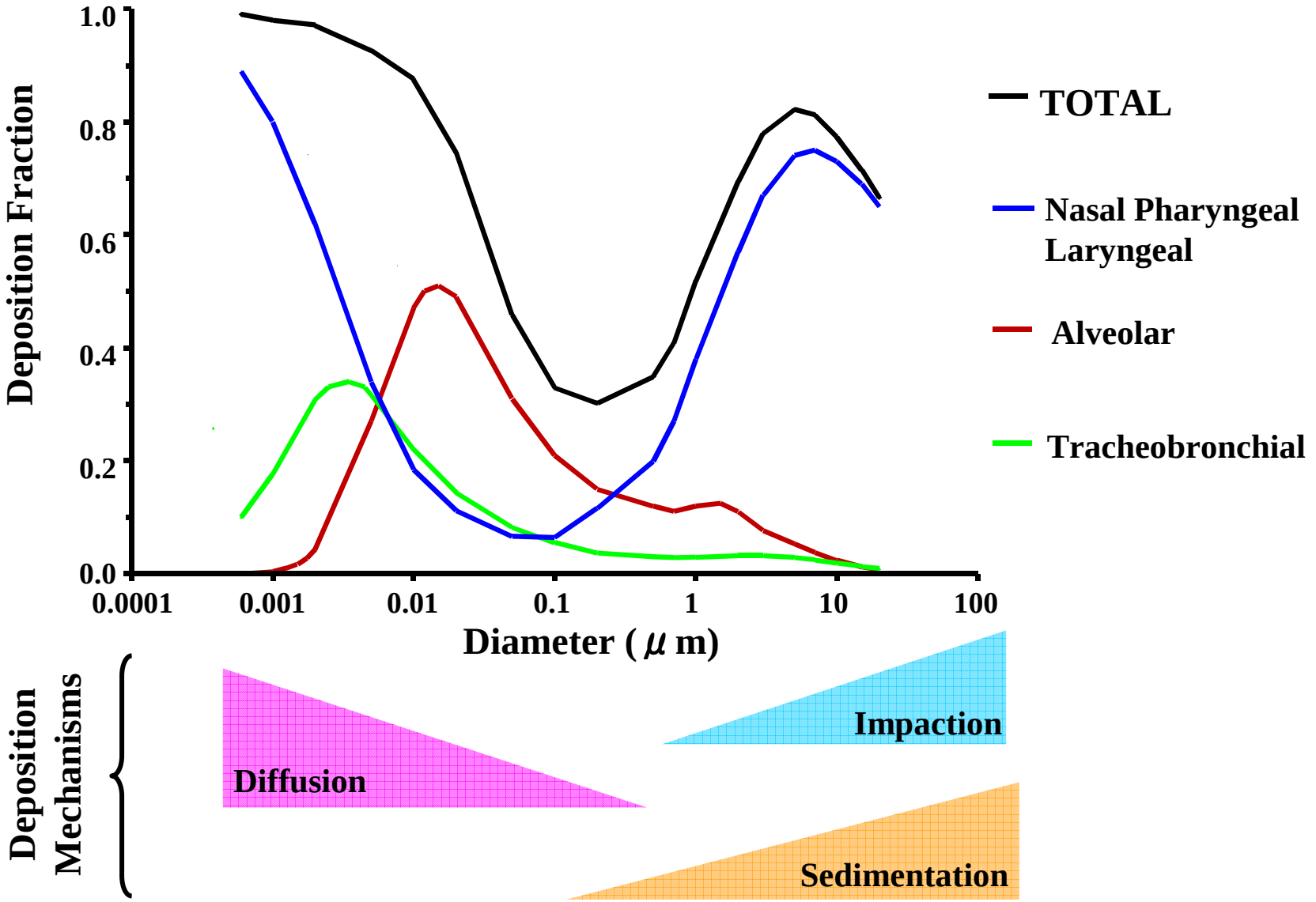
1. Vorbemerkungen Respirationstrakt Dosimetrie

2. Konzept Ableitung eines Luftgrenzwertes für Partikel am Arbeitsplatz von Ergebnissen einer chronischen Ratten Studie

3. Analyse der Akkumulations/Retentions Kinetik in der Lunge für eine Abschätzung der in vivo Löslichkeit und Toxizität inhalierter Metall-Partikel

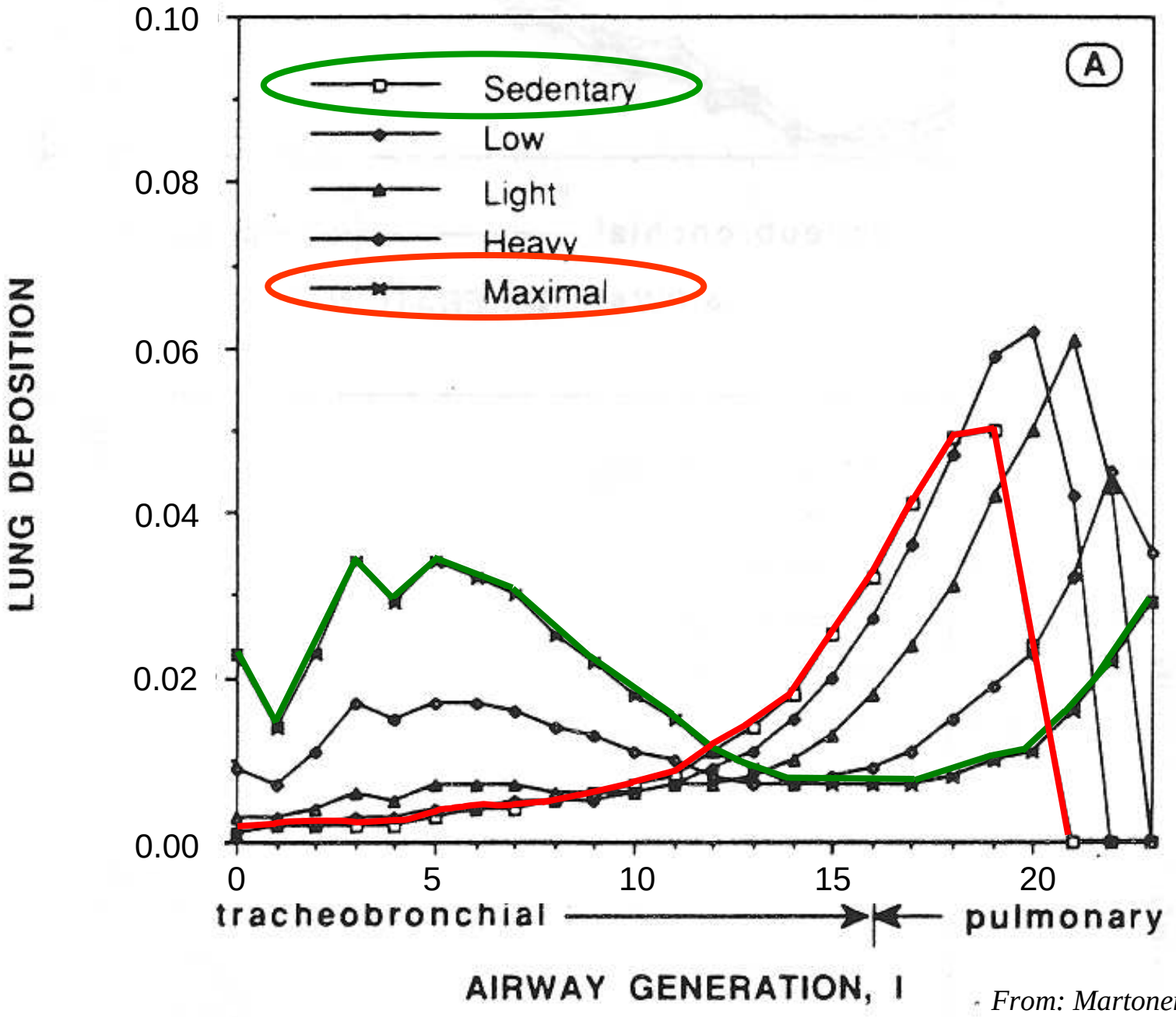
Regions of the Respiratory Tract





Oberdörster et al, 2006

Exercise and Deposition of Inhaled 2 µm Particles in Human Airways



From: Martonen et al., 1992

Respiratory Tract Toxicology
Exposure – Dose – Response Relationships

Dose: ≠ airborne concentration
≠ exposure

Inhaled dose: MV*(minute ventilation)* x conc. x time

Deposited dose: MV x conc. x time x dep. fraction
[volume x time^{-1} x mass x volume^{-1} x time]

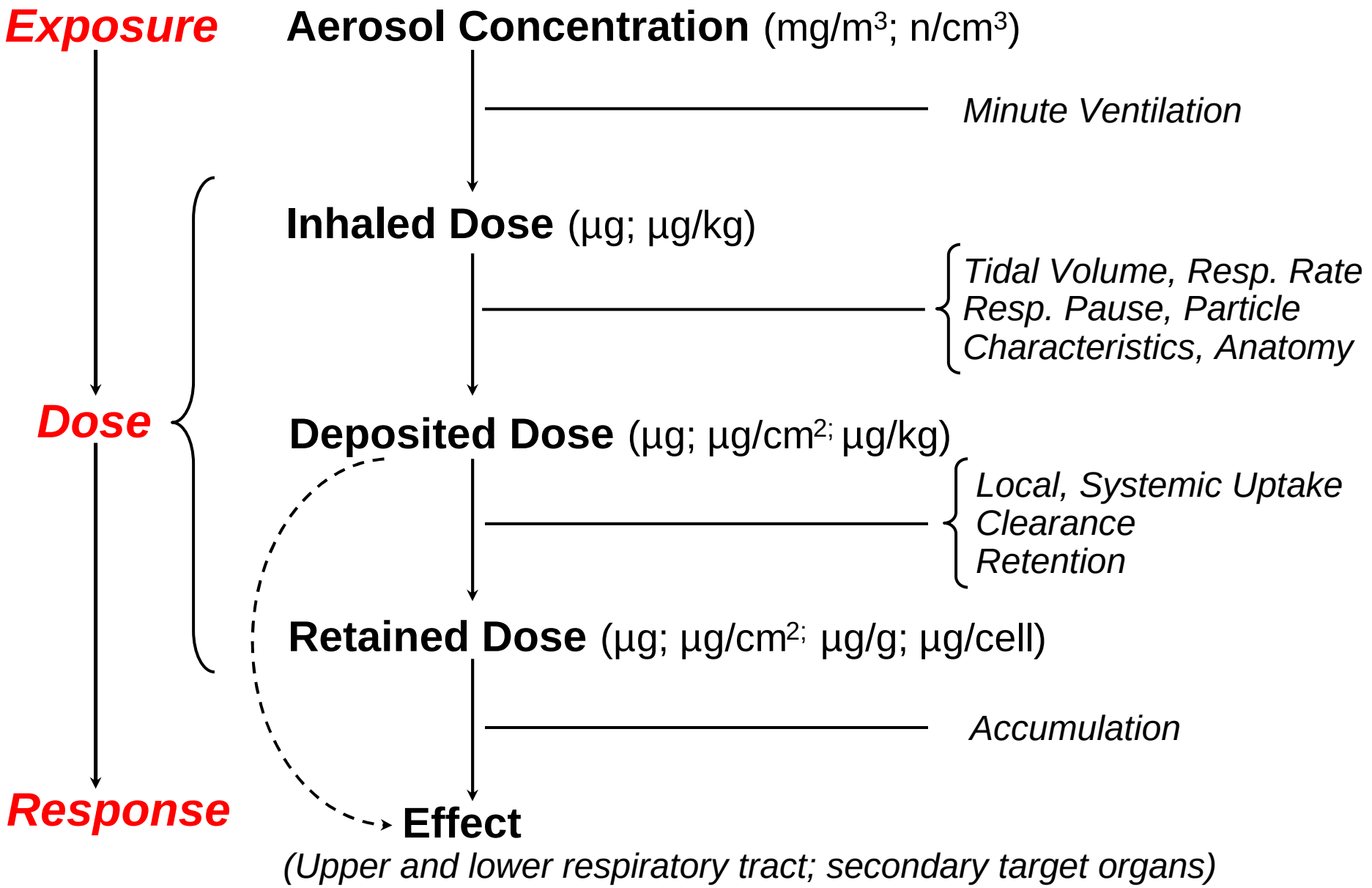
Retained dose: Remaining at some time after deposition
(Retention = Deposition – Clearance)

Dosimetry: Measurement (calculation) of dose

Dosemetric: parameter of dose *(e.g., particle mass, volume, number, surface area)*

Microdosimetry: Dose at cellular, subcellular level

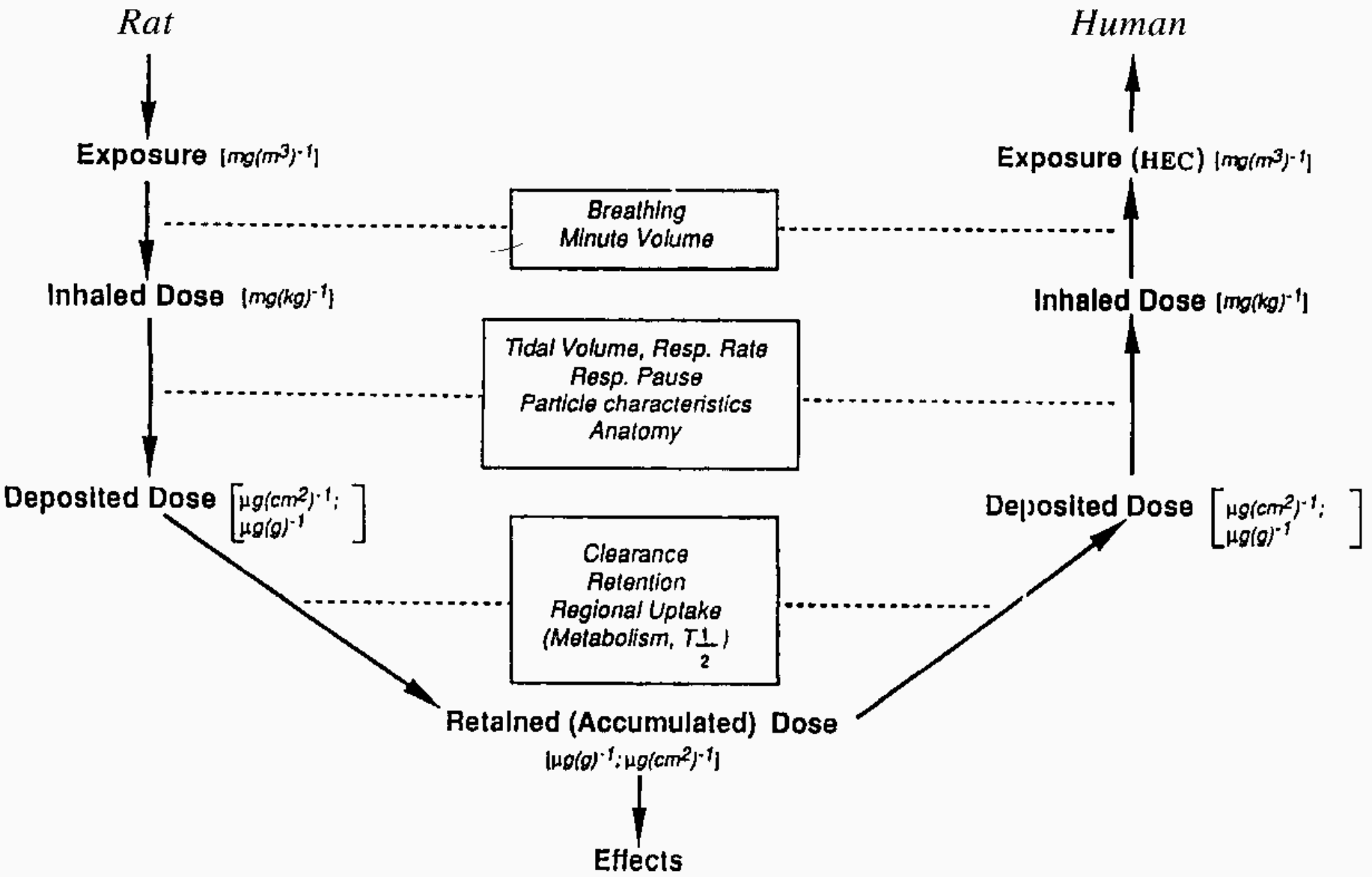
Factors Involved in Respiratory Tract Dosimetry



Surface Area of Respiratory Tract Regions

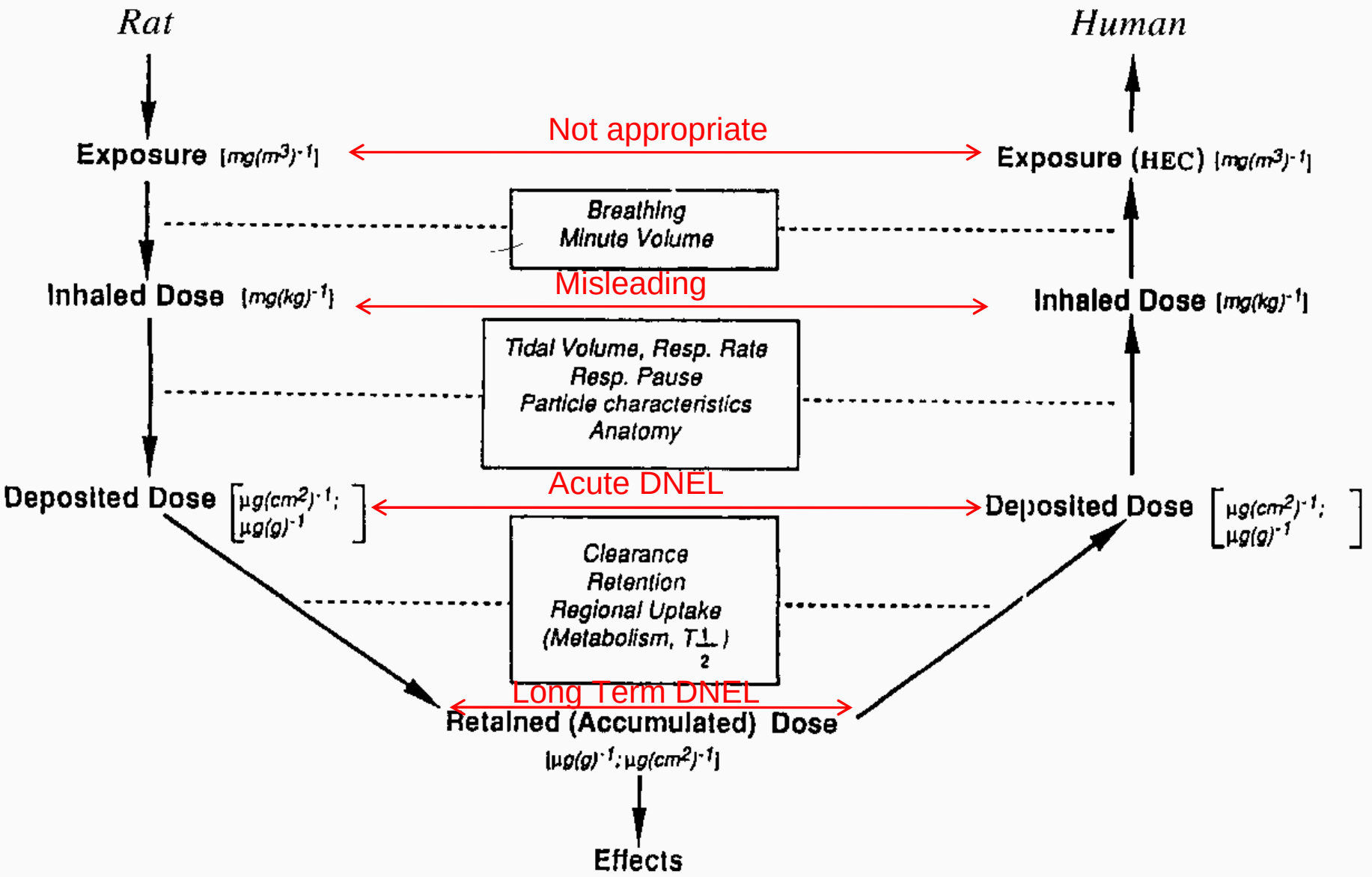
	Rat		Human	
	cm^2	*% of total*	*cm^2*	*% of total*
Nasal	***18.5***	***0.44***	***105***	***0.02***
Trach-bronch	***35***	***0.84***	***3200***	***0.54***
Alveolar	***4090***	***98.72***	***627000***	***99.44***

Dosimetric Extrapolation of Inhaled Particles from Rats to Humans



Assumption: If retained dose is the same in rats and humans, then effects will be the same

Dosimetric Extrapolation of Inhaled Particles from Rats to Humans



Assumption: If retained dose is the same in rats and humans, then effects will be the same

Multiple Path Particle Deposition Model (MPPD)

(Asgharian et al, 1999)

Human Model

5-Lobar Yeh-Schum Model; Stochastic Model; Age Specific Model

FRC = 3300 cm^3; URT = 50 cm^2

Particle Parameter: MMAD; MMD; CMD; GSD; Concentration

Inhalability Adjustment; Nanoparticle Model; Gravity

Different Body Orientations: Upright; Prone; Supine; Right/Left Side

Tidal Volume; Breathing Frequency; Inspiratory Fraction and Pause

Breathing Scenario: Nasal; Oral; Oro-Nasal; Endotracheal

Deposition only; Deposition and Clearance

Bronchial and slow, medium, fast Alveolar Clearance

Exposure Times and Duration; Post Exposure Time

Multiple Path Particle Deposition Model (MPPD)

(Asgharian et al, 1999)

Rat Model

Asymmetric Multiple Path

FRC = 4.0 cm^3; URT = 0.42 cm^3

Particle Parameter: MMAD; MMD; CMD; GSD; Concentration

Inhalability Adjustment; Nanoparticle Model; Gravity

Different Body Orientations: Upright; Prone; Supine; Right/Left Side

Tidal Volume; Breathing Frequency; Inspiratory Fraction and Pause

Breathing Scenario: Nasal; Endotracheal

Deposition only; Deposition and Clearance

Bronchial and slow, medium, fast Alveolar Clearance

Exposure Times and Duration; Post Exposure Time

Ableitung von Expositions-Standard

Beispiel: Chronische (2 Jahre) Ratten Inhalation, TiO_2

(Muhle et al., 1991; Bellman et al., 1991)

F-344 Ratten; Rutile TiO_2; 6 St/Tag; 5 Tage/Woche;

MMAD = 1,1 µm; GSD = 1,6; Konz.: 5 mg/m³; Spez Dichte: 4,3 g/cm³

TiO_2 Akkumulation in der Lunge:

Monat:	***3***	***9***	***15***	***21***	***24***
mg/Lunge:	***0,91 ±0,22***	***1,53 ±0,19***	***2,02 ±0,34***	***2,97 ±0,71***	***3,20 ±0,44***

Ableitung einer HEC basierend auf:

A: Deponierte Dosis pro Tag

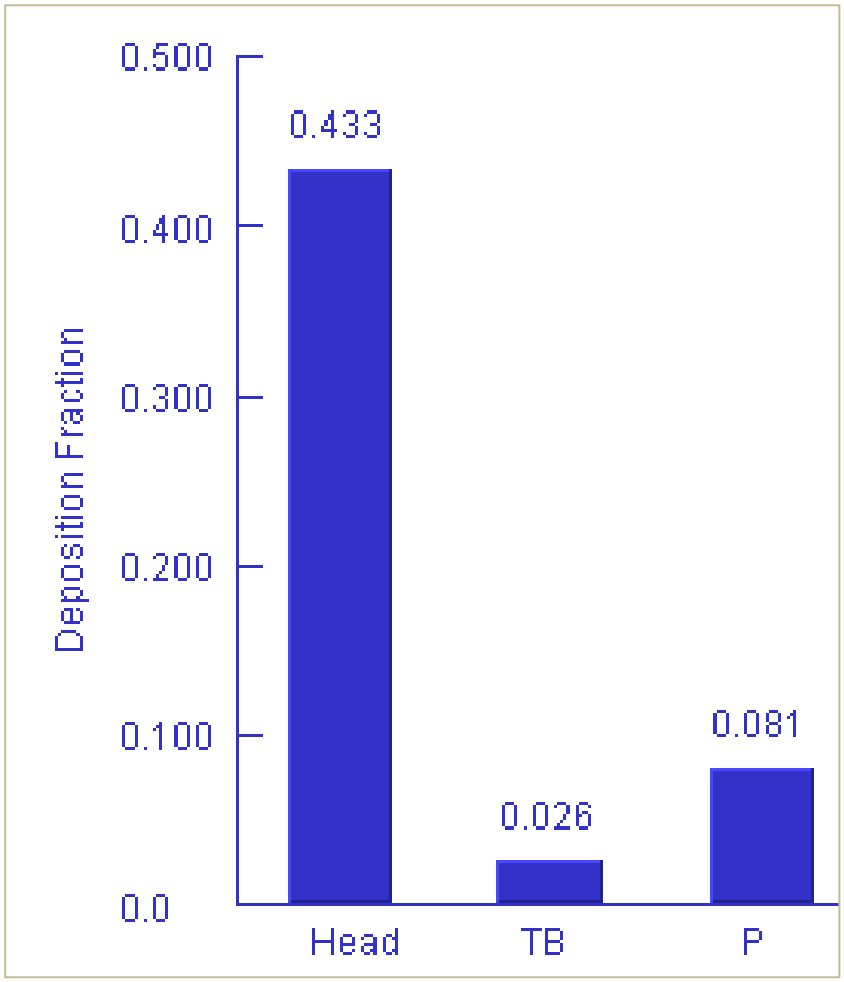
Ratte: 45 µg/day

B: Retinierte Dosis, nach 2 Jahren:

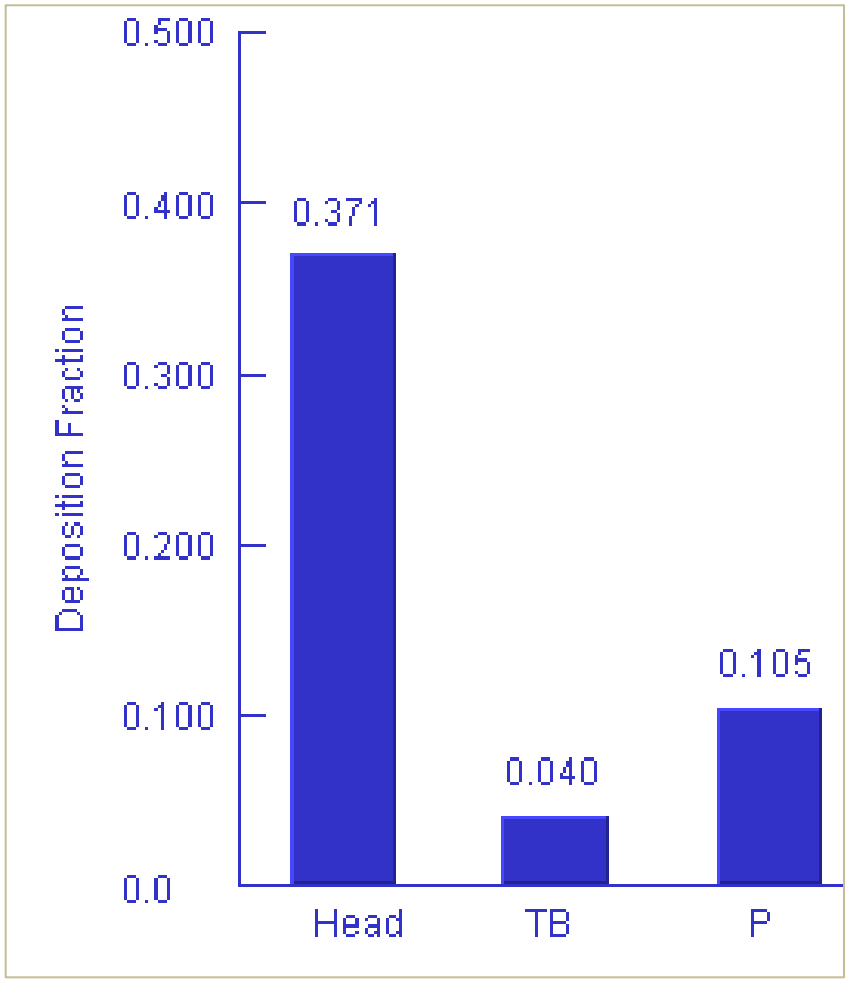
Ratte: 3.2 mg/Lunge

TiO_2 Inhalation, Deposition Efficiency for MMAD = 1.1 µm with GSD = 1.6

RAT



HUMAN



Ratte-Mensch dosimetrische Extrapolation, HEC,
basierend auf gleicher deponierter Masse pro cm^2 alveolare Oberfläche:

Alveoläre Oberfläche: Ratte = 4090 cm^2 Mensch = 627000cm^2

Ratte: **Äquivalente Masse pro Oberflächeneinheit deponiert an einem Tag:**

Pro Oberfläche deponiert: Ratte: 45 µg ÷ 4090 = 11 ng/cm^2

= Äquivalenz-Oberflächen Dosis für Mensch deponiert an einem Tag

Mensch: **Gesamt Deposition in Human-Lunge pro 8-Stunden Tag unter**

Annahme leichter Arbeit: TV = 1024 ml; AF = 20/min

Inhalierte TiO_2 Konzentration um 11 ng/cm^2 zu erreichen:

6,7 mg/m^3

Ratte-Mensch dosimetrische Extrapolation, HEC,
basierend auf gleicher retinierter Masse pro cm^2 alveoläre Oberfläche:

Alveoläre Clearance Raten: **Ratte = 0,01/Tag *(70 Tage $T_{1/2}$)***
Mensch = 0,001/Tag *(700Tage $T_{1/2}$)*

Ratte: **TiO_2 pro Oberflächeneinheit retiniert nach 2 Jahren in der Ratte:**
Ratte: 3200 µg ÷ 4090 cm^2 = 0,78 µg/cm^2
= Äquivalenz-Oberflächen Dosis für Mensch nach 40 Jahren

Mensch: **Gesamt Retention nach 40 Jahren Berufs-Exposition in Lunge**
unter Annahme leichter Arbeit: 8 Stunden/Tag, 230 Tage/Jahr;
TV = 1024 ml; Atemfrequenz = 20/min

490,6 mg/Lunge

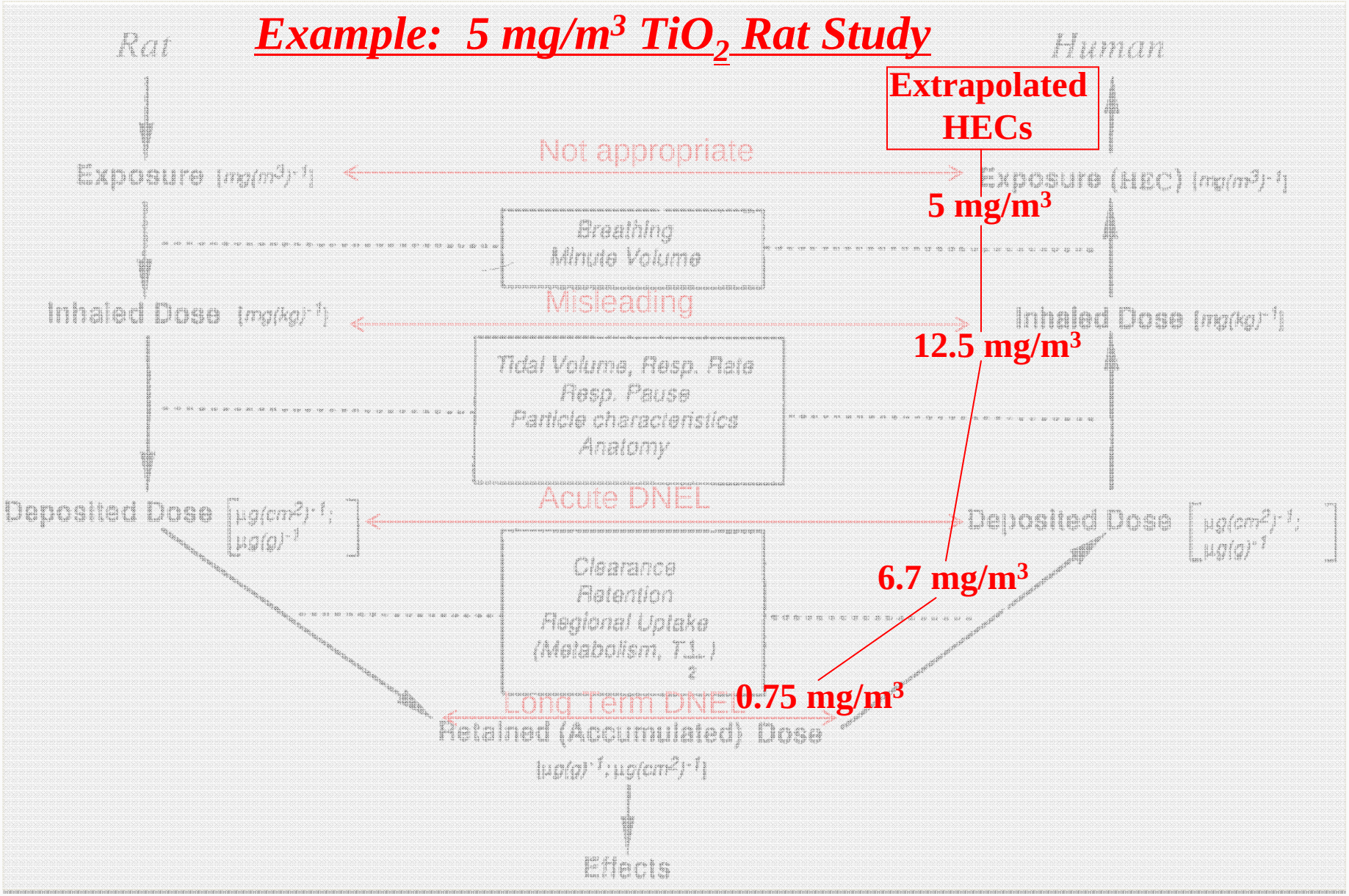
Tägliche deponierte TiO_2 Masse um diesen Wert zu erreichen:

770 µg/Lunge

Inhalierte Arbeitsplatz Konzentration, die nach 40 Jahren
0,78 µg/cm^2 alveolar Oberfläche beim Mensch erreicht:

750 µg/m^3

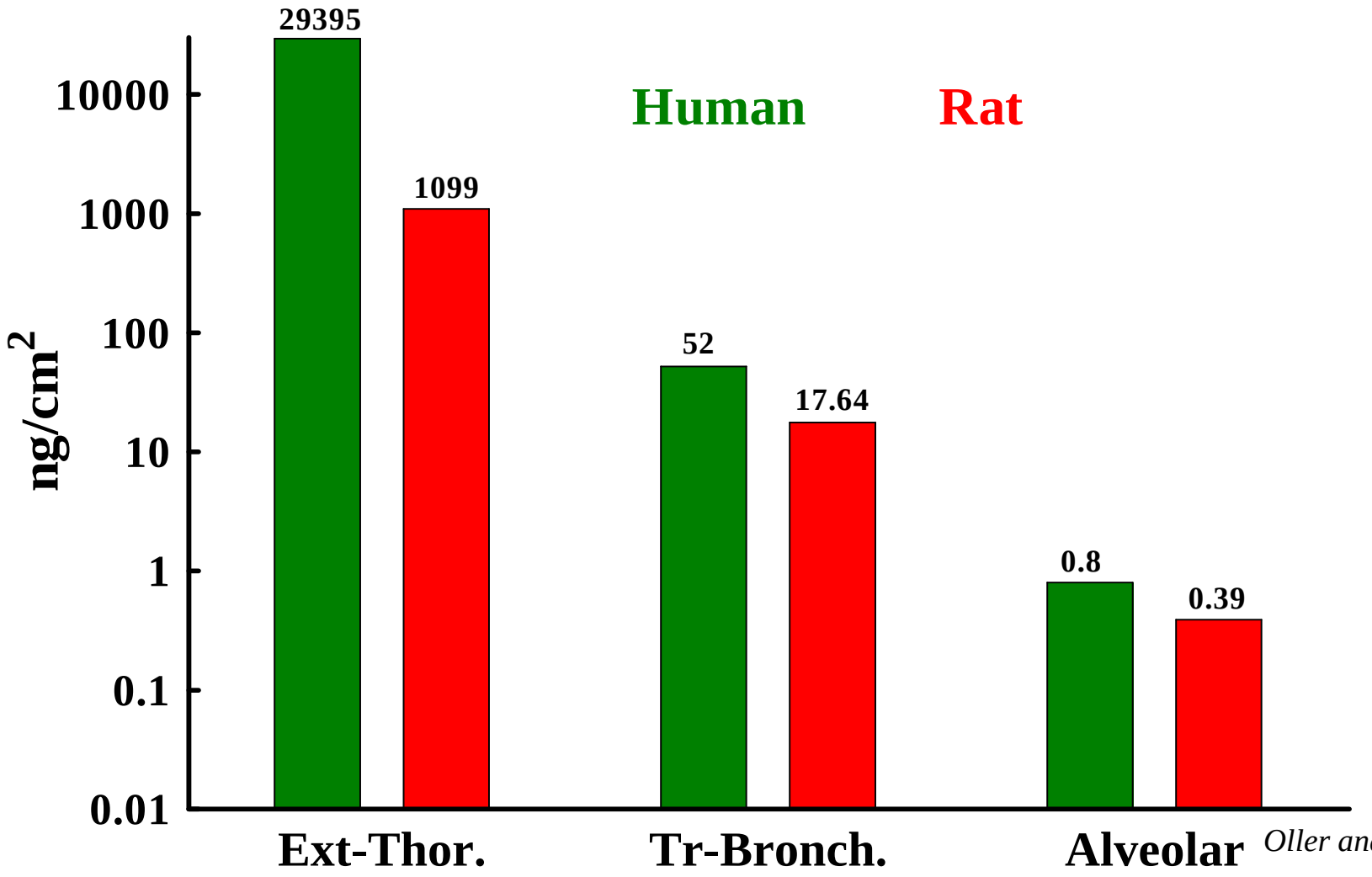
Dosimetric Extrapolation of Inhaled Particles from Rats to Humans



Assumption: If retained dose is the same in rats and humans, then effects will be the same

Deposition per Unit Surface Area (cm^2) over 6 (rat) or 8 (human) Hours at 500 $\mu g/m^3$ (NiO)

Human and rat data: MMAD=2.21μm
GSD=1.97

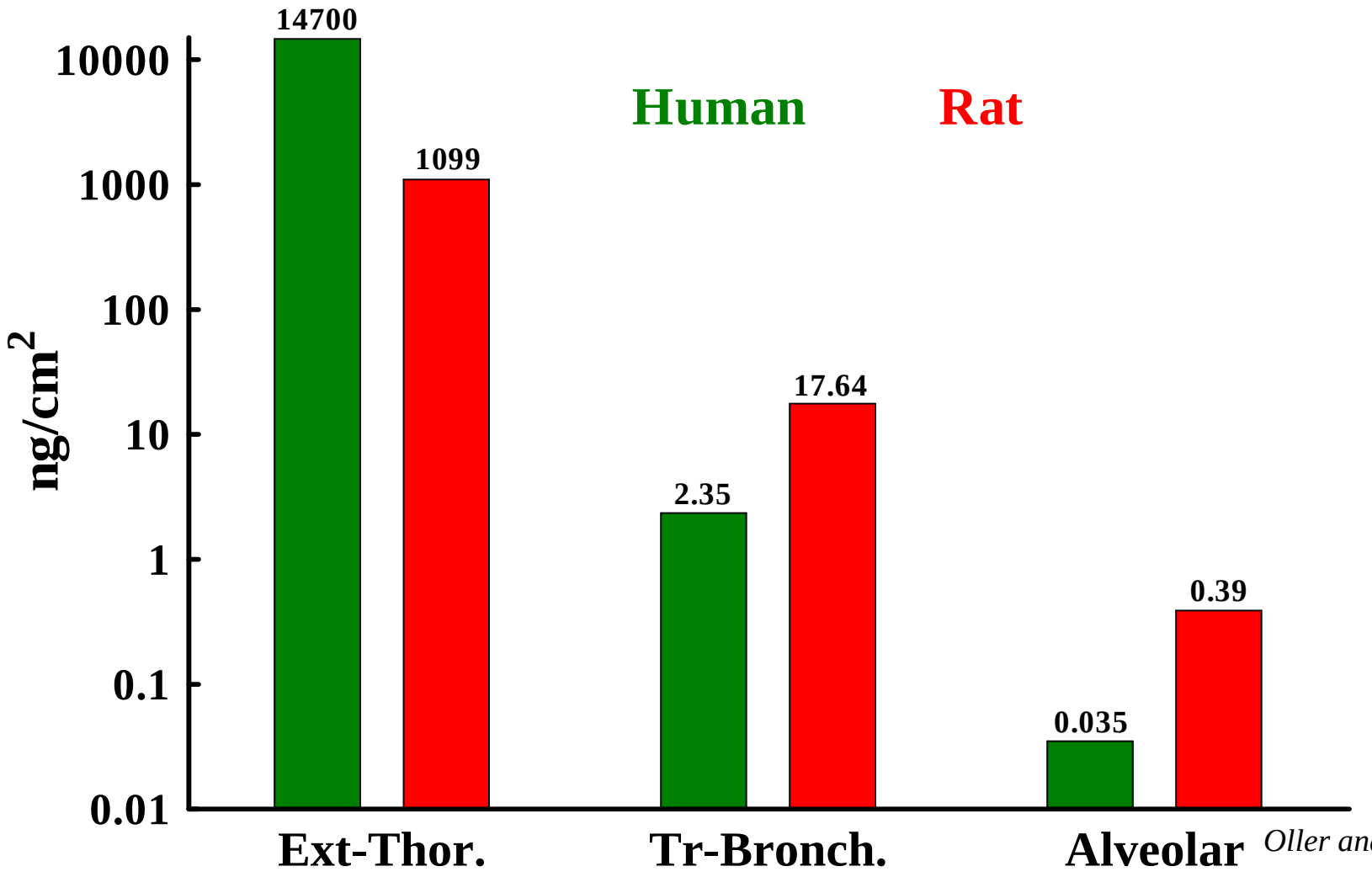


Oller and Oberdörster, 2010

Deposition per Unit Surface Area (cm^2) over 6 (rat) or 8 (human) Hours at 500 $\mu g/m^3$ (NiO)

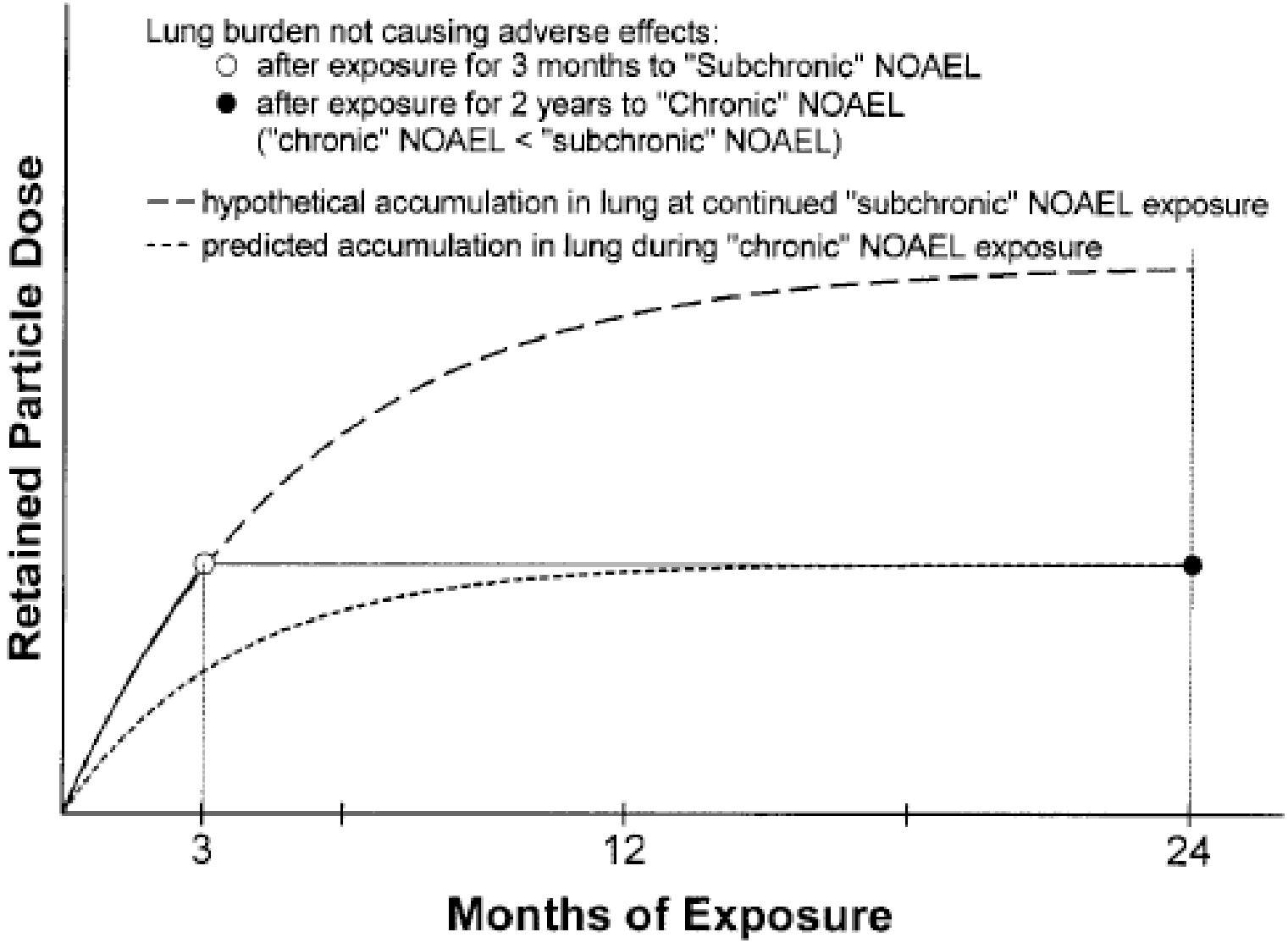
Human data: MMAD=61.22 um GSD=3.52

Rat data: MMAD=2.21μm GSD=1.97



Oller and Oberdörster, 2010

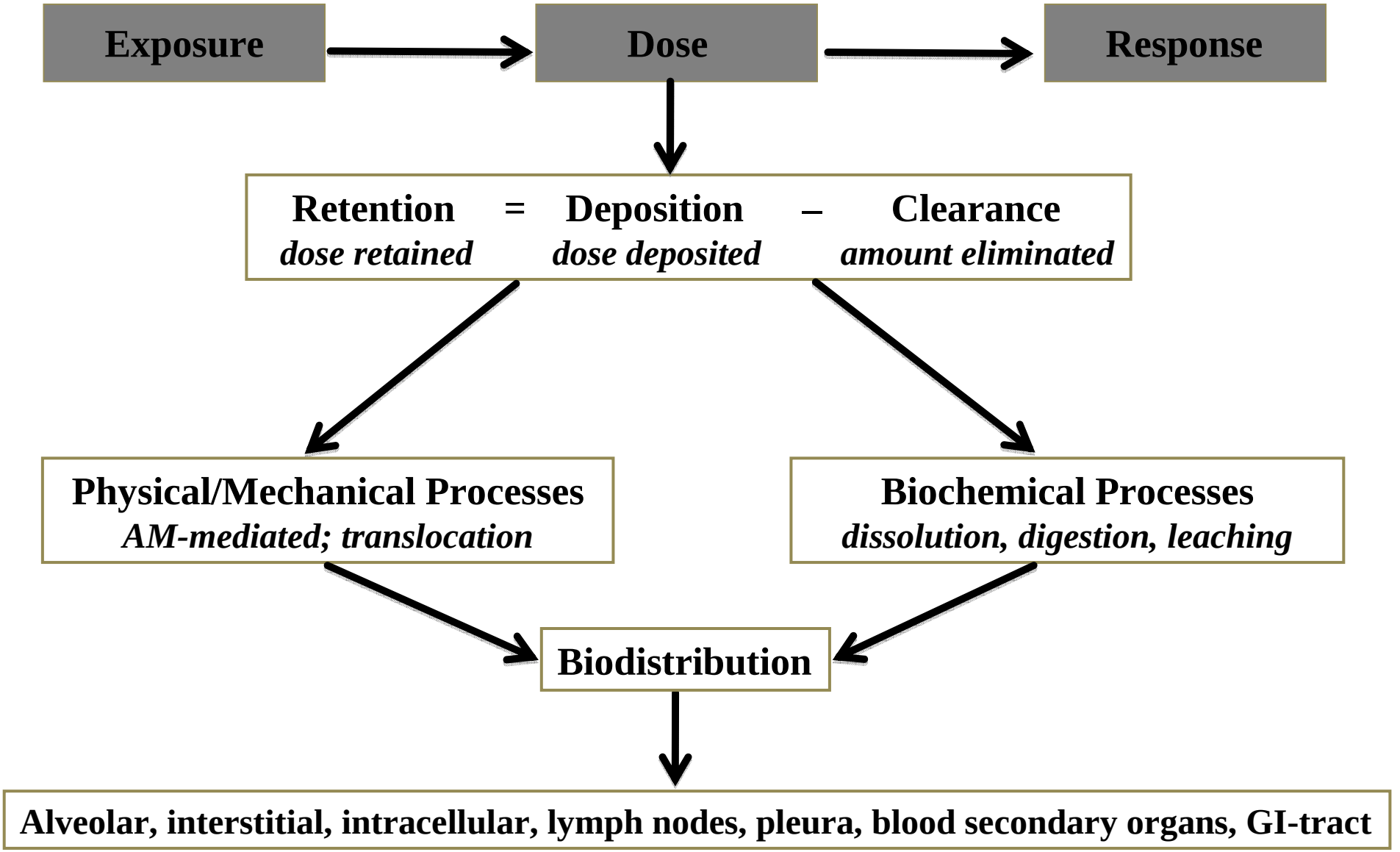
Estimation of NOAEL from Subchronic Study



From: Oberdörster, 2002

In Vivo Löslichkeits-Rate

Determinants of Biokinetics of Inhaled Particles



Clearance of Inhaled particles: Separating mechanical and dissolution clearance

Determining Dissolution:

Approaches:

- ***in vitro*: simulated lung fluid, extra-, intra-cellular; static/dynamic system**

- ***in vivo*:**
  - **lung clearance data and analyze together with blood levels**
  - **compare lung buildup of particle in question with that of a poorly soluble particle of low cytotoxicity (PSP) with same physical characteristics**

Clearance of Inhaled particles: Separating mechanical clearance and dissolution

Lung accumulation, assuming first order kinetics:

$$A_t = \frac{a}{b} \times \frac{5}{7} (1 - e^{-bt})$$

A_t = accumulated lung burden at time (t)

a = daily deposited amount (MPPD model)

b = clearance rate; $\frac{ln2}{b} = T1/2$

Total clearance rate = mechanical clearance rate + dissolution rate

$$b_{tot} = b_{mech} + b_{sol}$$

$$\frac{1}{T1/2_{tot}} = \frac{1}{T1/2_{mech}} + \frac{1}{T1/2_{sol}}$$

Clearance of Inhaled particles: Separating mechanical and dissolution clearance

In Vivo Second Approach:

Available:

Results from chronic rat inhalation study; 6 hrs/day, 5 days/wk, 1-2 years

Exposure concentration; MMAD; GSD; spec. density ρ

Lung burden buildup over 6 months to 2 years

Calculation:

assume PSP with same physical particle parameters as study particle

model buildup of PSP over study duration,

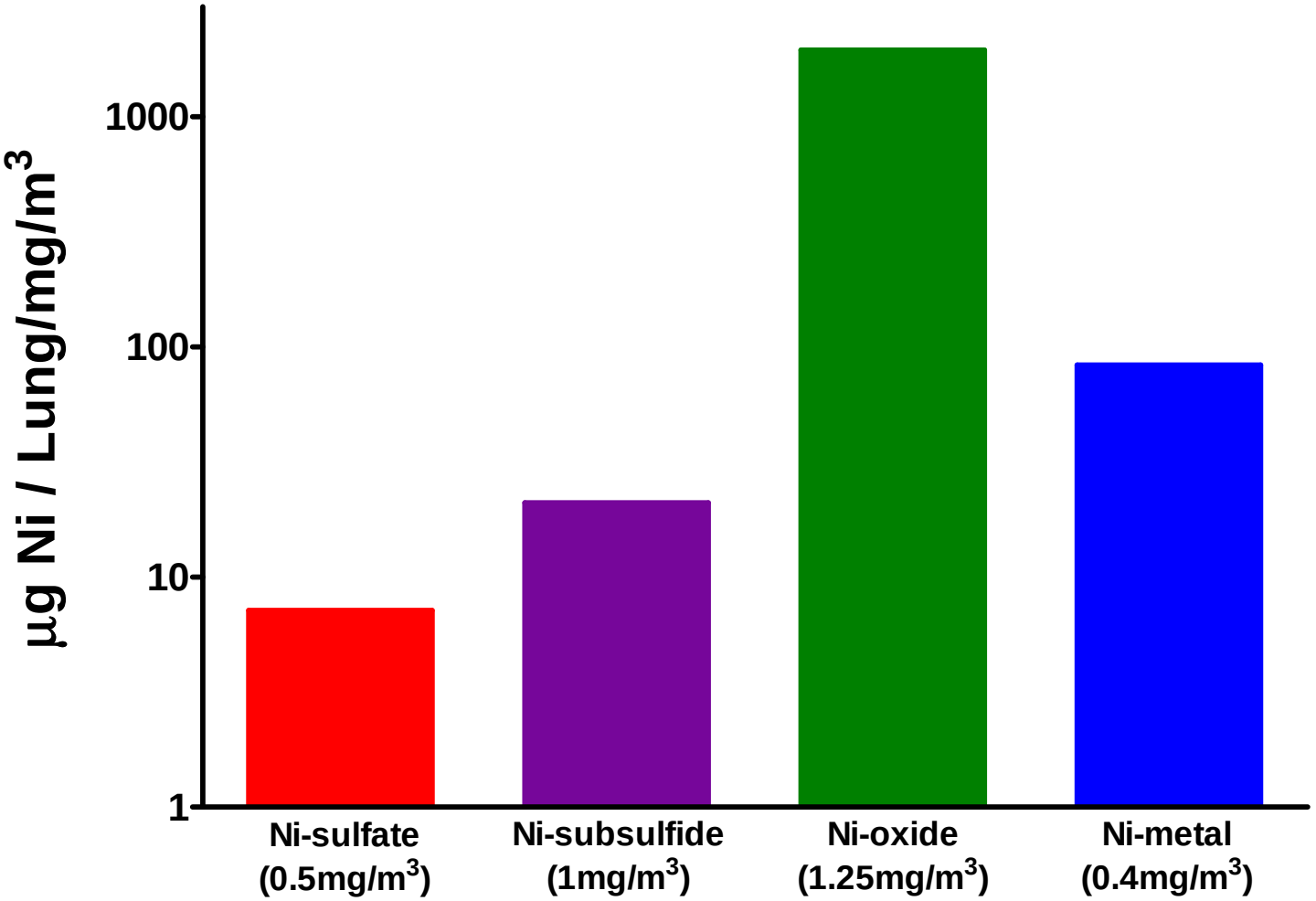
for PSP: (*e.g.*, TiO2) **$T_{1/2_{mech}}$ = 70 days** (clearance rate b = 0.01/day)

$T_{1/2_{sol}}$ = 0

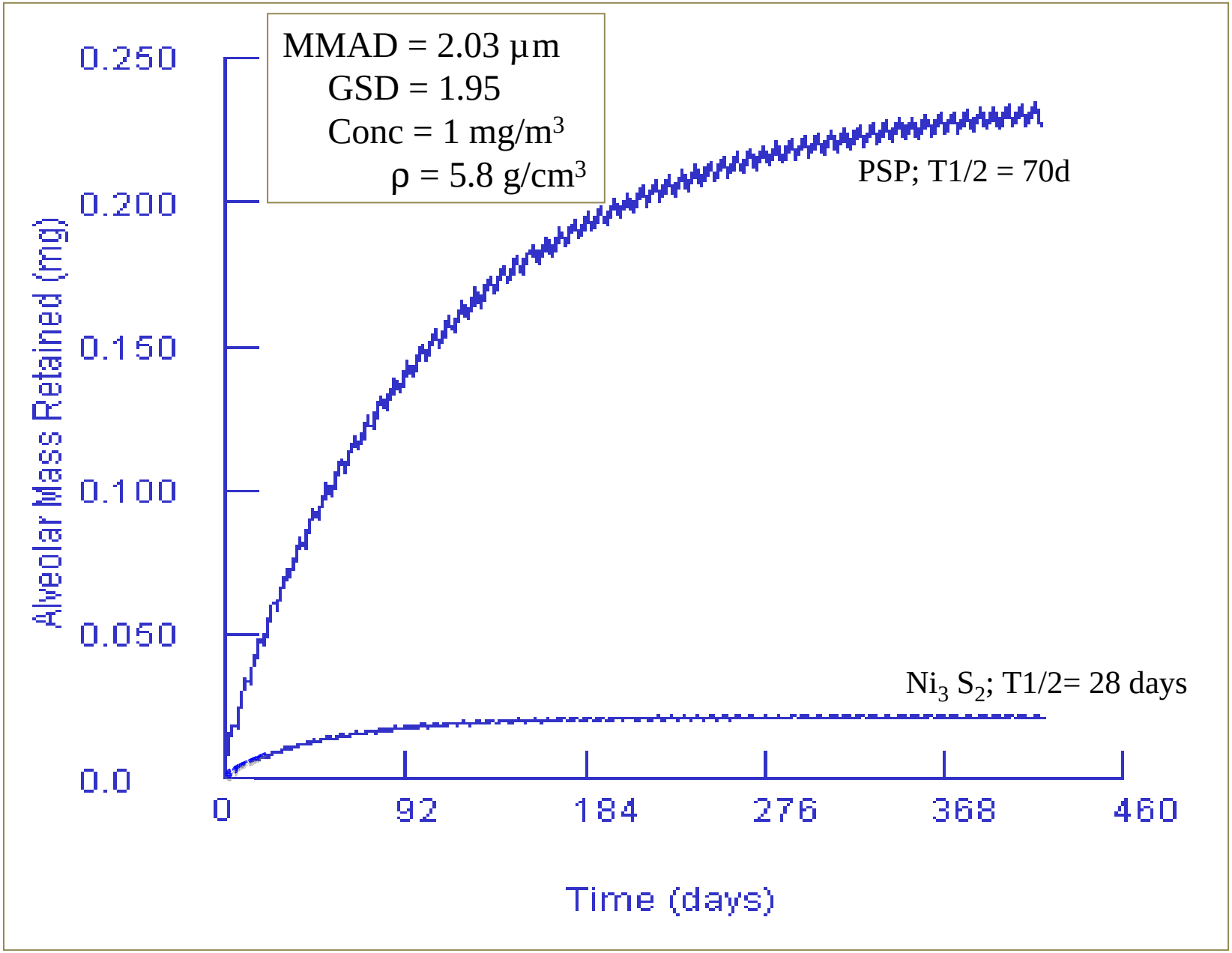
Compare to actual retention halftime ($T_{1/2}$) and clearance rate (b) of study particle

Normalized Retained Lung Burden at 15 Months of Exposure

(12 months for Ni-metal)



$Ni_3 S_2$ Chronic Rat Inhalation Study:
Comparing actual lung retention with PSP of same physical particle characteristics



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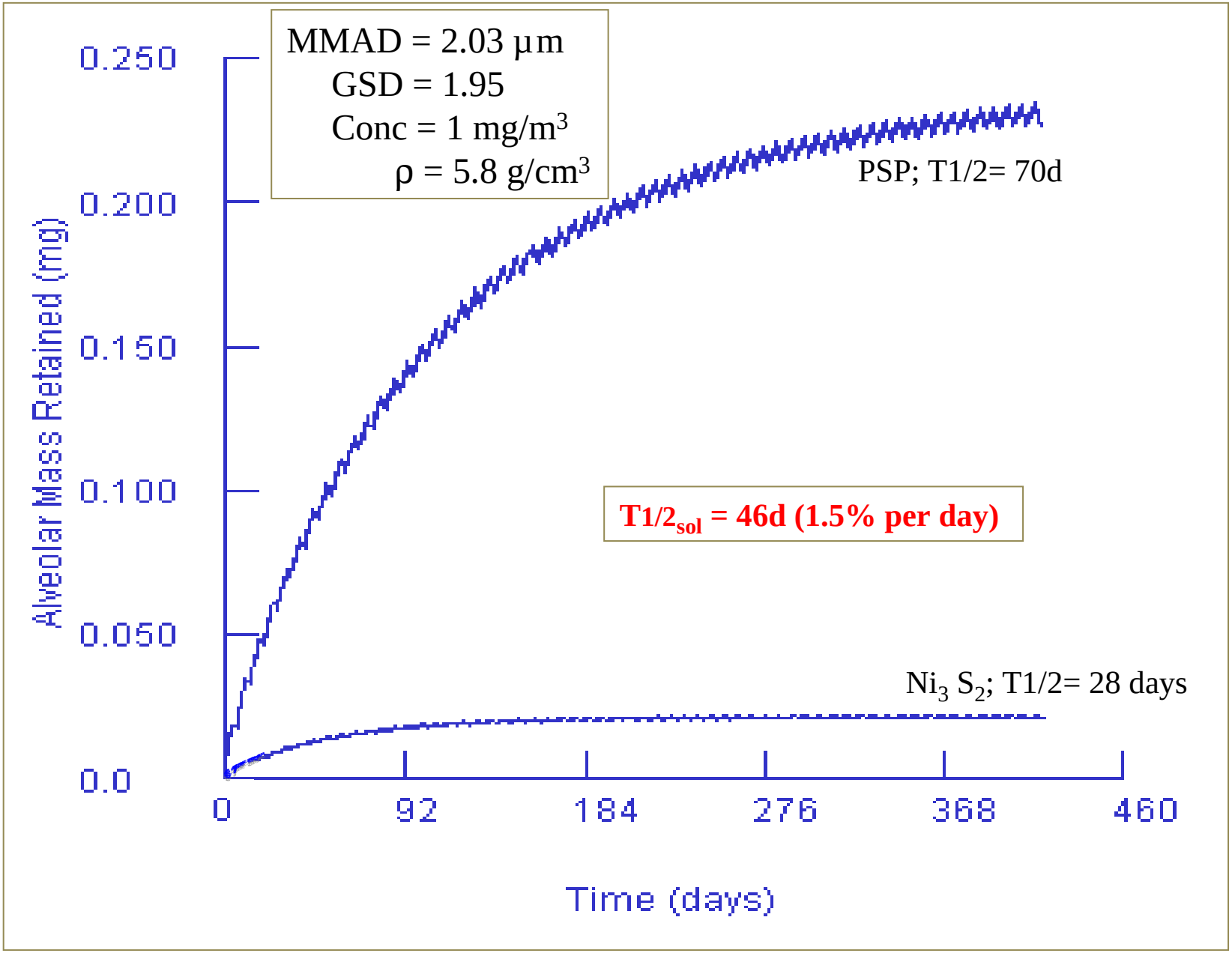
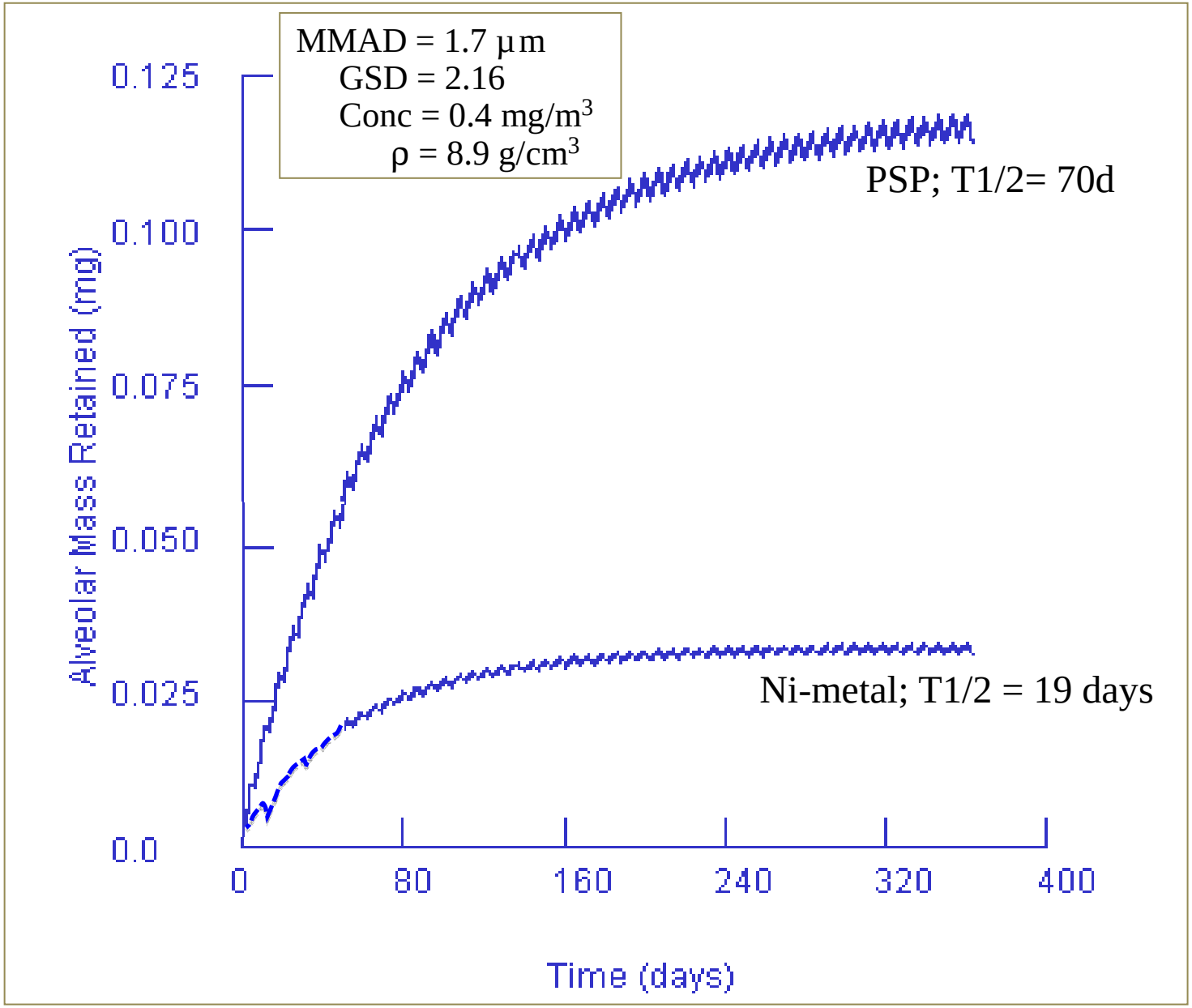


Ni-Metal Chronic Rat Inhalation Study:
Comparing actual lung retention with PSP of same physical particle characteristics



Ni-Metal Chronic Rat Inhalation Study:
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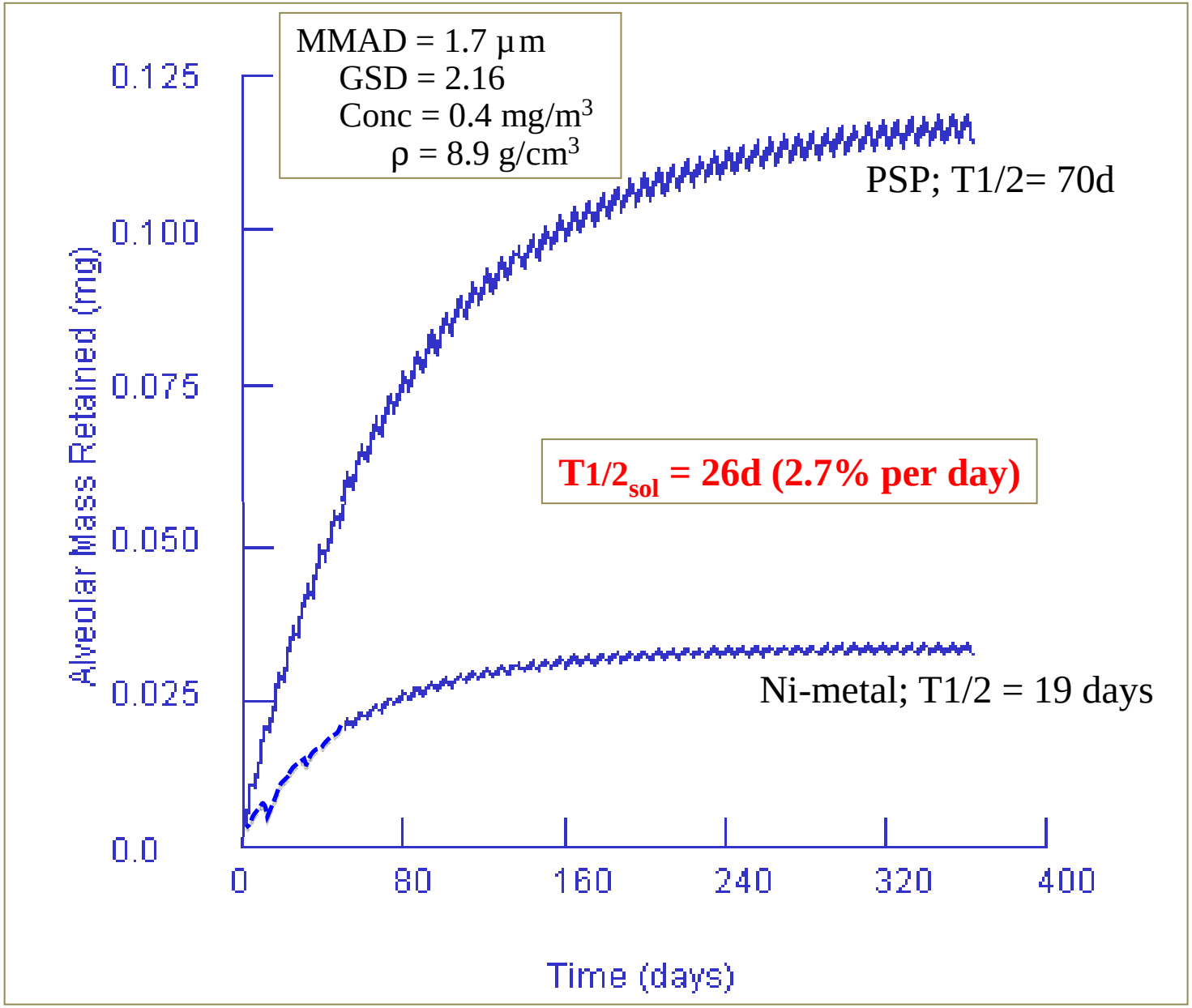
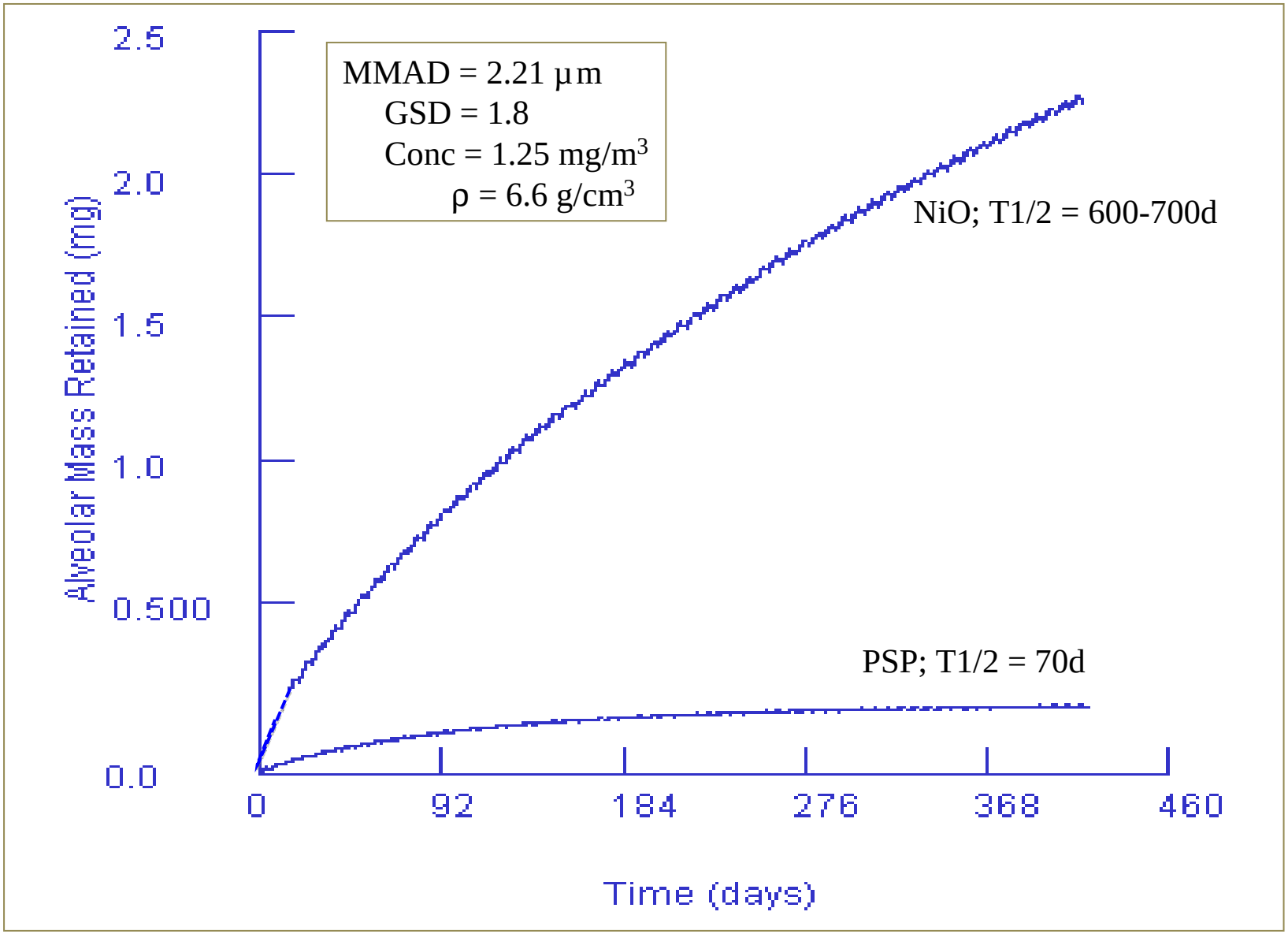


NiO Chronic Rat Inhalation Study:
Comparing actual lung retention with PSP of same physical particle characteristics



***In Vivo* Löslichkeit inhalierter Metall-Partikel lässt sich durch Vergleich der Retention mit PSP abschätzen.**

<u>Aber</u>:

- **Die Clearance Rate könnte signifikant durch Bindung des gelösten Metalls an Zellstrukturen** (Proteine) **beinflusst werden.**

- **Vergleich mit löslichen Metall-Verbindungen ist hilfreich.**

- **Annahme ist, dass $T1/2_{sol}$ ist gleich in der Lunge von Ratte und Mensch.**