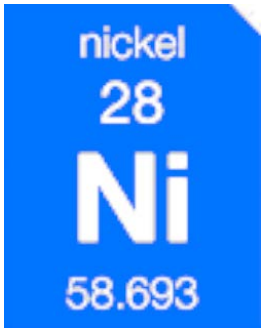
Data Availability and Metal-Related Risk Assessment Issues: Nickel



June 12, 2013

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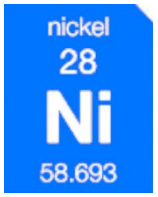
NiPERA Inc. Nickel Producers Environmental Research Association

Nickel INSTITUTE

Outline

- Data availability and bioaccessibility-based read-across
- Incorporation of dosimetry into RfC derivation
- Incorporation of absorption into RfD derivation

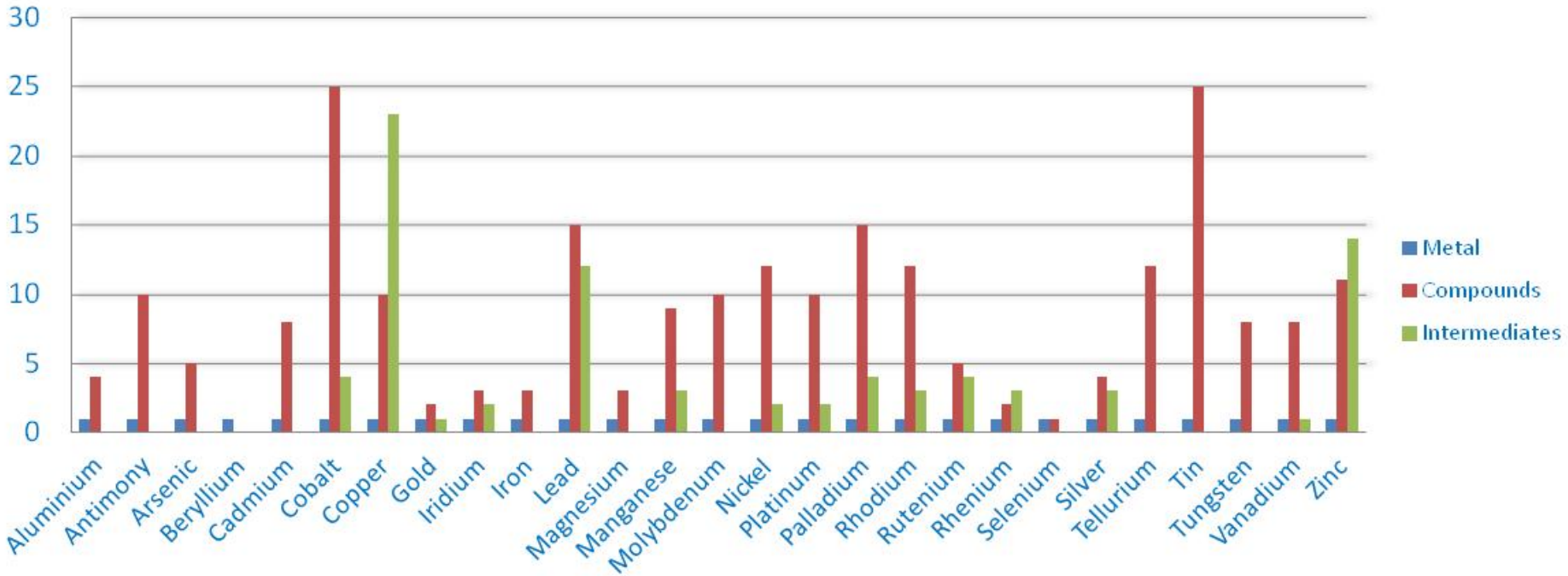


Data availability and bioaccessibility-based read-across

Metal Substances Registered in 2010

nickel
28
Ni
58.693

Source: REACH Metals Gateway (www.reach-gateway.eu)



REACH Registration of Ni Metal & 10 Ni Compounds

Fortunately, we had fairly complete datasets for 4 substances (Reference Substances)

nickel
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Ni
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Toxicity Endpoint for GHS Classification	Nickel Sulphate	Nickel Chloride	Nickel Nitrate	Nickel Oxide (Black & Green)	Nickel Hydroxy-carbonate	Nickel Dihydroxide	Nickel Sulphamate	Nickel Acetate	Nickel Subsulfide	Nickel Sulphide	Nickel Metal
Dermal Irritation/Skin Corrosion (GHS)											
Eye Irritation											
Dermal Sensitization											
Acute Oral Toxicity											
STOT-SE (oral)											
Acute Inhalation Toxicity											
STOT-SE (inhalation)											
Acute Dermal Toxicity											
STOT-SE (dermal)											
Chronic Toxicity/STOT-RE (oral)											
Chronic Toxicity/STOT-RE (dermal)											
Chronic Toxicity/STOT-RE (inhalation)											
Reproductive Toxicity											
Respiratory Sensitization											

REACH Registration of Ni Metal & 10 Ni Compounds

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How do we apply read-across from reference to data-poor substances?

Toxicity Endpoint for GHS Classification	Nickel Sulphate	Nickel Chloride	Nickel Nitrate	Nickel Oxide (Black & Green)	Nickel Hydroxy-carbonate	Nickel Dihydroxide	Nickel Sulphamate	Nickel Acetate	Nickel Subsulfide	Nickel Sulphide	Nickel Metal
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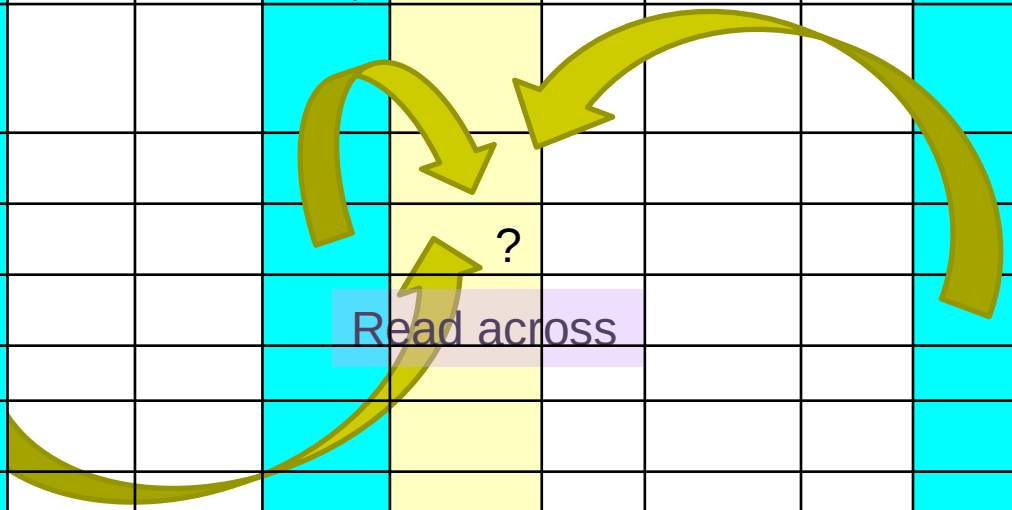
Respiratory Sensitization											



Example: Oral Route and Systemic Effects

nickel
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Ni
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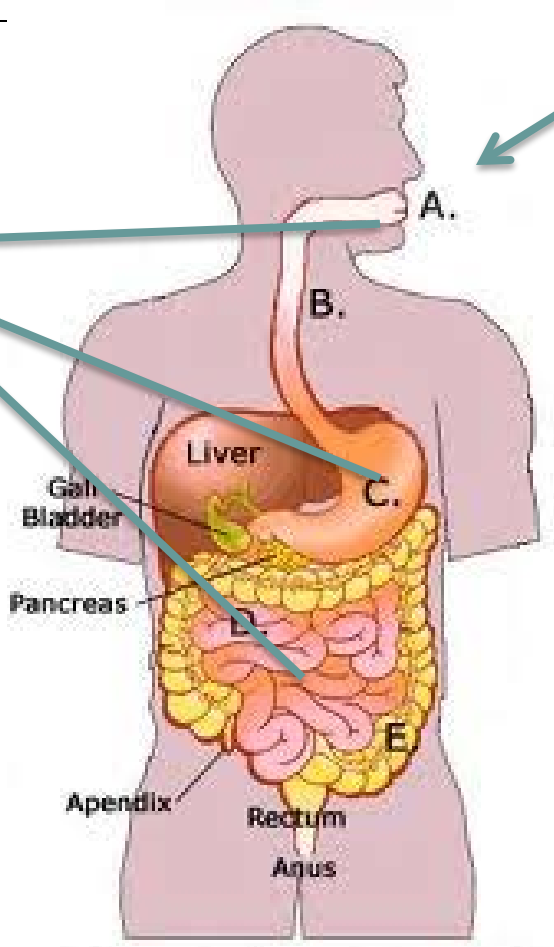
Metal Substance

Systemic absorption

Bioavailable Metal Ion

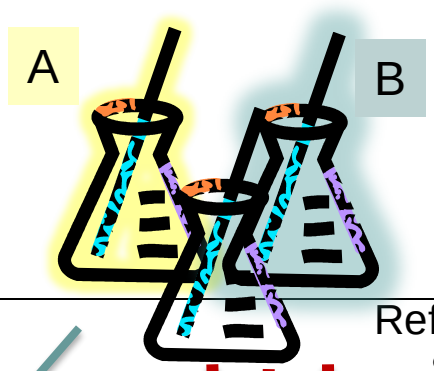
Systemic effects



Bioavailability is the extent to which a substance is taken up by an organism and is available for metabolism and interaction

Bioavailability of Metal Ion is part of the weight of evidence approach applied to read-across !

Example: Oral Route



Reference Metal Substance

Saliva

Gastric fluid

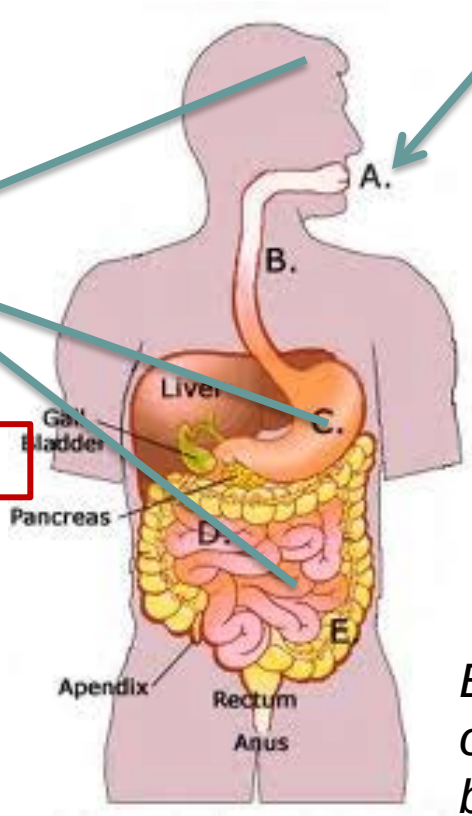
Intestinal fluid

Bioaccessible Metal Ion

Systemic absorption

Bioavailable Metal Ion

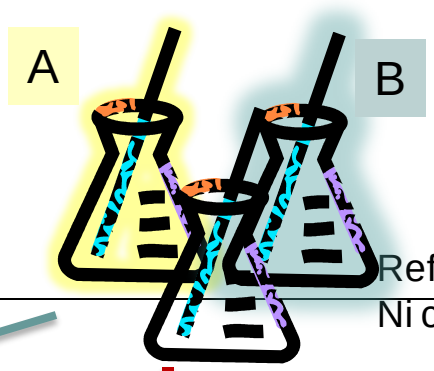
Systemic effects



Bioaccessibility indicates the extent of metal ion release in synthetic biological fluids that is available for contact or for potential absorption

Bioaccessibility provides a conservative estimate of bioavailability

Read- Across Steps
Example: Ni & Oral Route

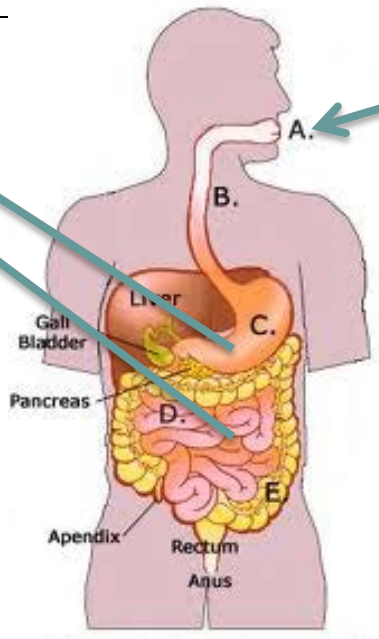


Reference Ni compound

Systemic absorption

Bioavailable Ni $^{2+}$

Systemic effects



Saliva

Gastric fluid

Intestinal fluid

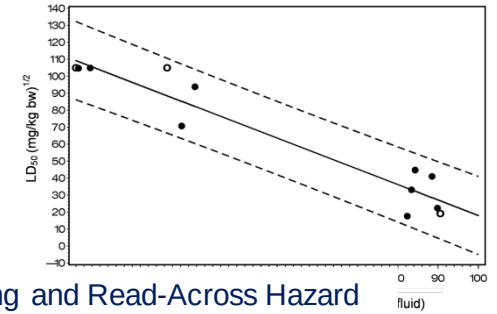
1: Generate Ni ion release data for reference & target (data-poor) substances

Bioaccessible Ni $^{2+}$

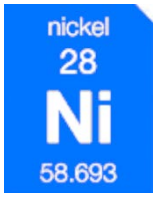
2: Incorporate in vivo toxicokinetic & toxicity data to verify that bioac-cessibility correlates with bioavailability

3: Group target substances & identify appropriate reference substances based on relative Ni bioaccessibility data

4: Read-across toxicological data from reference to target Ni substances



Henderson, RG, Cappellini D, Seilkop SK, Bates HK and Oller AR, 2012. Oral Bioaccessibility Testing and Read-Across Hazard Assessment of Nickel Compounds. *Regul Toxicol and Pharmacol*. Volume 63, pages 20–28.



Incorporation of dosimetry into RfC derivation

Health Effects-Related Aerosol Fractions

nickel
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Ni
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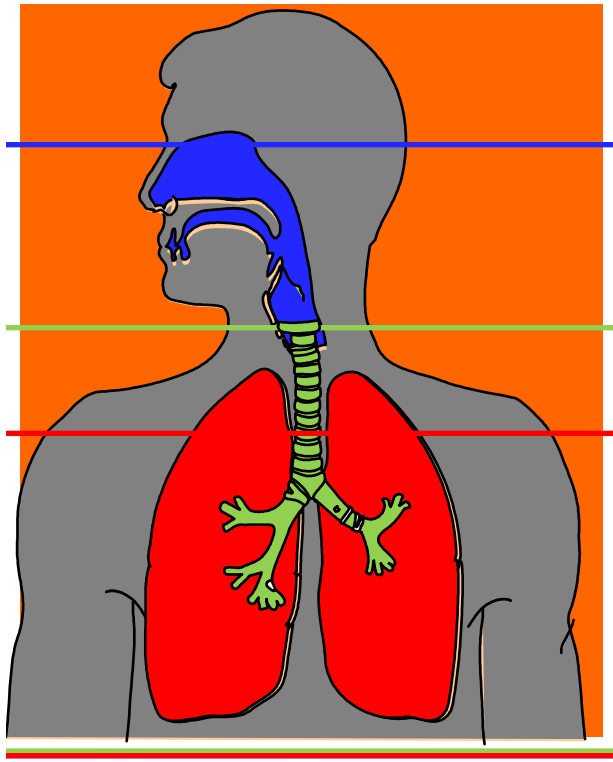

Respiratory Tract

Extrathoracic
(nose irritation)

Tracheo-bronchial
(asthma)

Alveolar
(fibrosis)

Deposition

Health-based aerosol fractions & samplers

nickel
28
Ni
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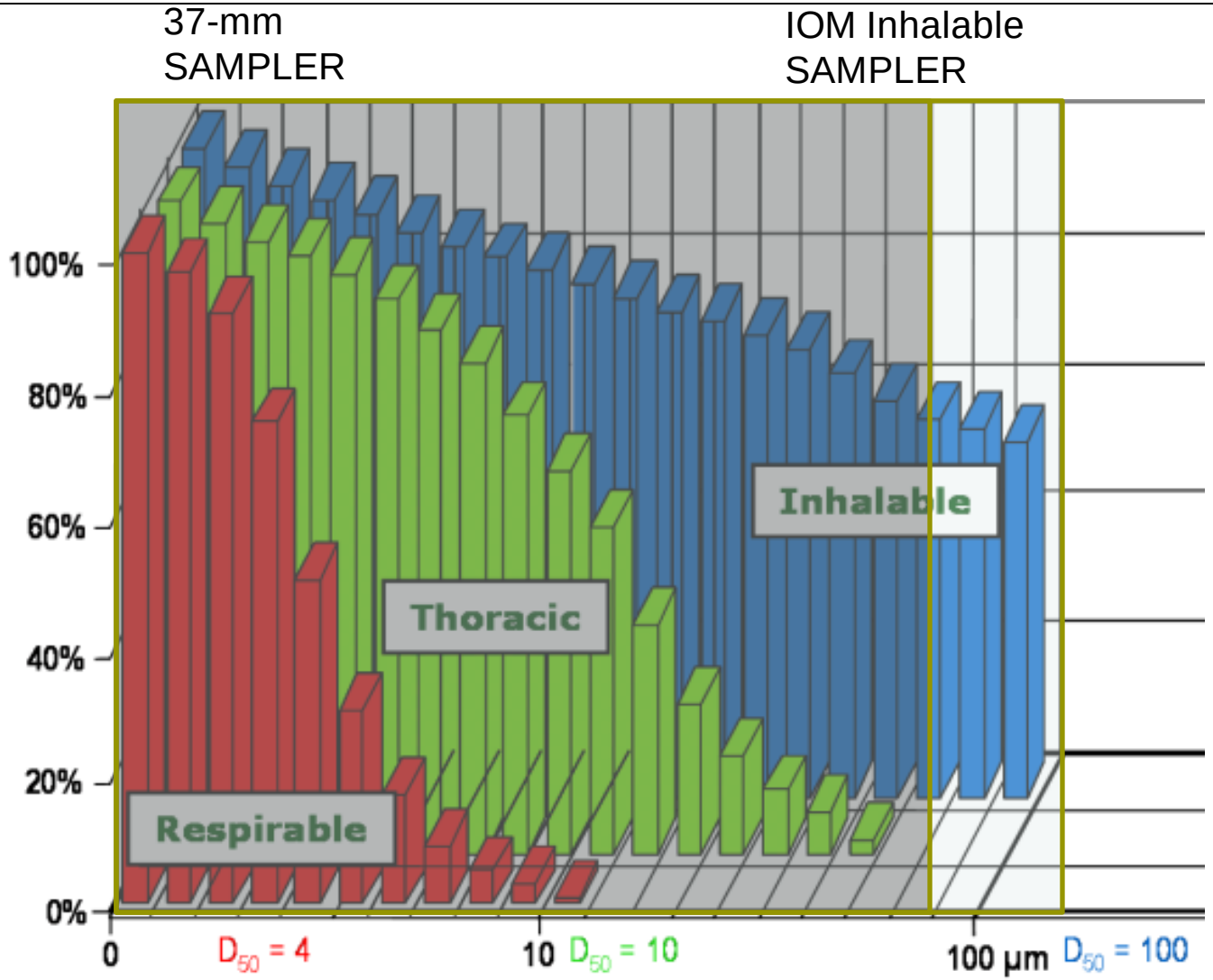
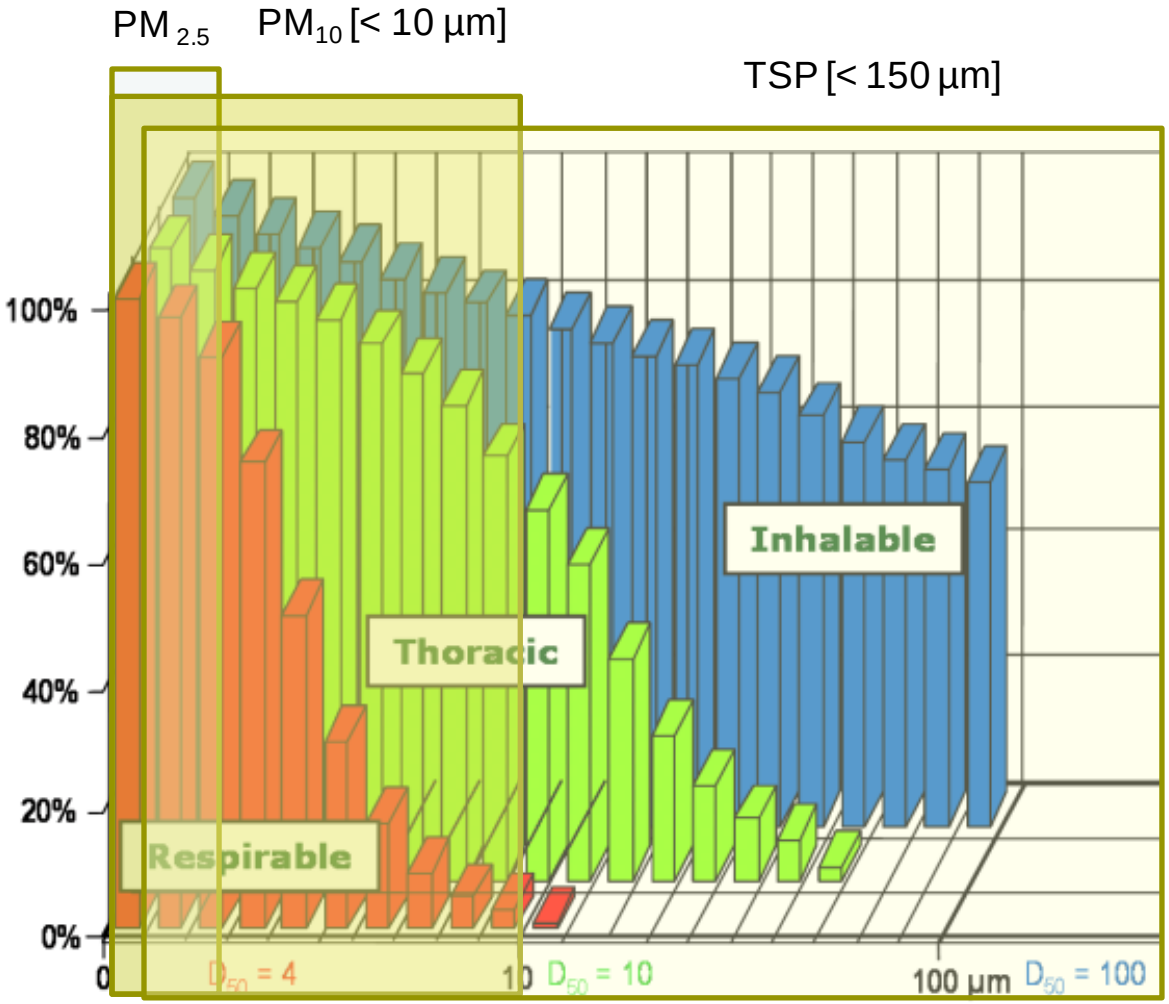


Health-based aerosol fractions & samplers



TSP=total suspended particulate

Particle Size Extrapolation

Exposure ?

Respirable

Exposure (mg Ni/m^3)

Inhaled Dose

Deposited Dose

Retained Dose -Alveolar region-

Effects: toxicity

Exposure (mg Ni/m^3)

Inhaled Dose

Deposited Dose

Respirable Human Equivalent

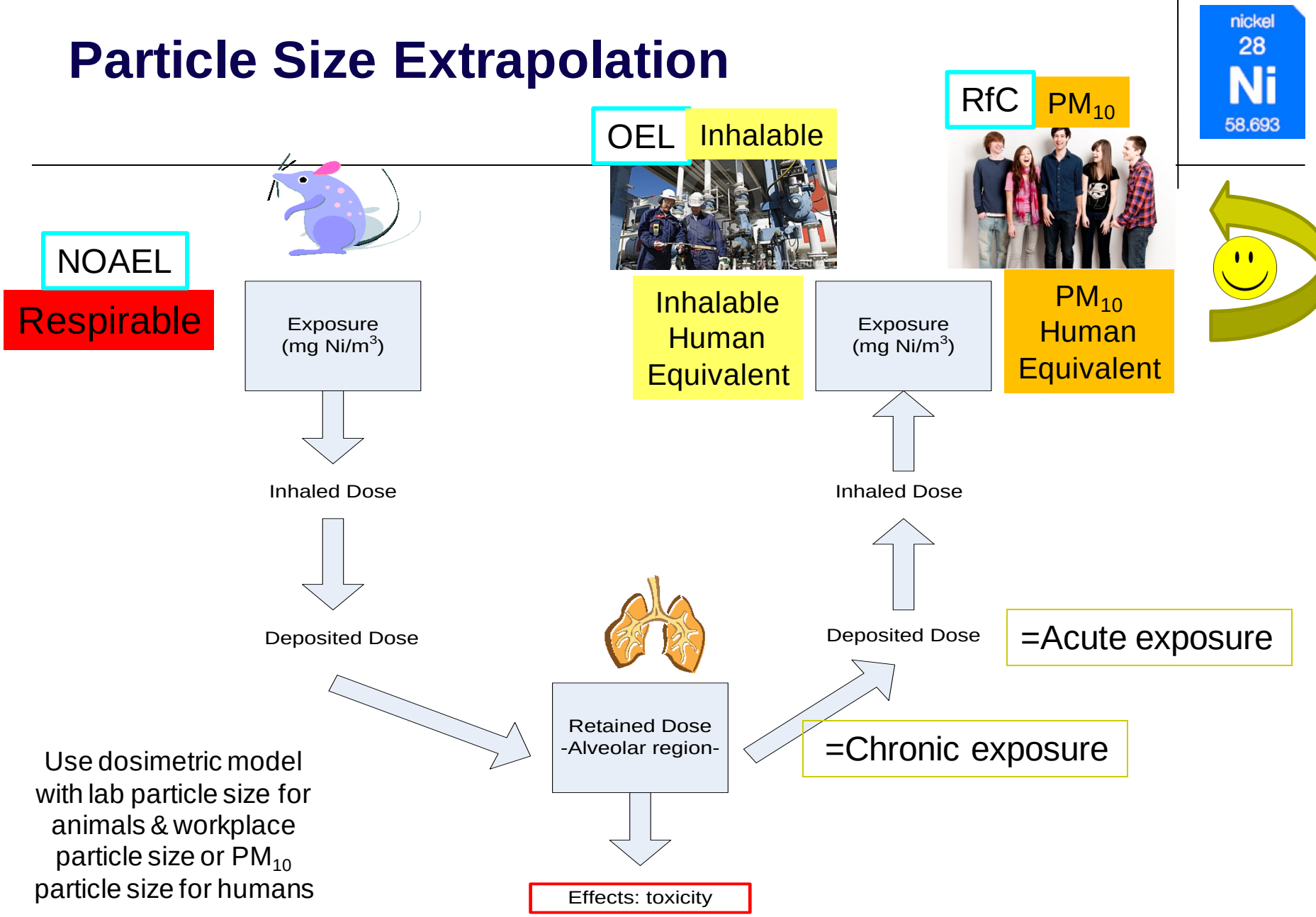
=Acute exposure

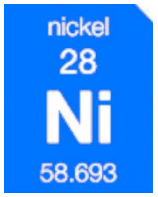
=Chronic exposure

Use dosimetric model with same particle size for animals and humans

Oller AR, Oberdörster G. Incorporation of particle size differences between animal studies and human workplace aerosols for deriving Exposure limit values. Regul Toxicol Pharmacol. 2010 Jul-Aug;57(2-3):181-94.

Particle Size Extrapolation





Incorporation of bioavailability into RfD derivation

Oral Route and Systemic Effects: RfD

nickel
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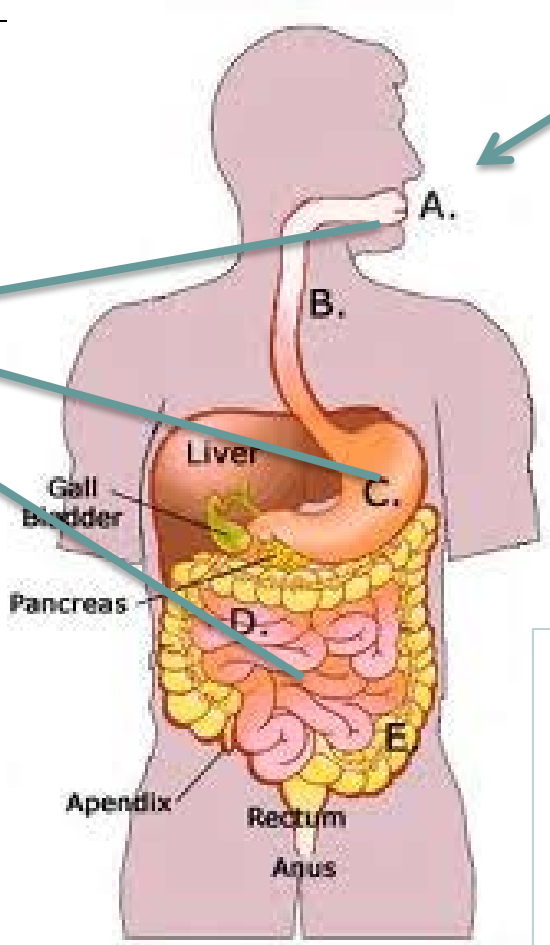
Metal Substance
External RfD

systemic absorption in reference study

Bioavailable Metal Ion
-bioavailable RfD-

Systemic effects observed in reference study



Example

Oral absorption of Ni^{2+} is different:

- For water soluble and insoluble forms
- From food or from water
- From water with empty or full stomach
- From different Ni-containing soils

Oral Route and Systemic Effects: RfD

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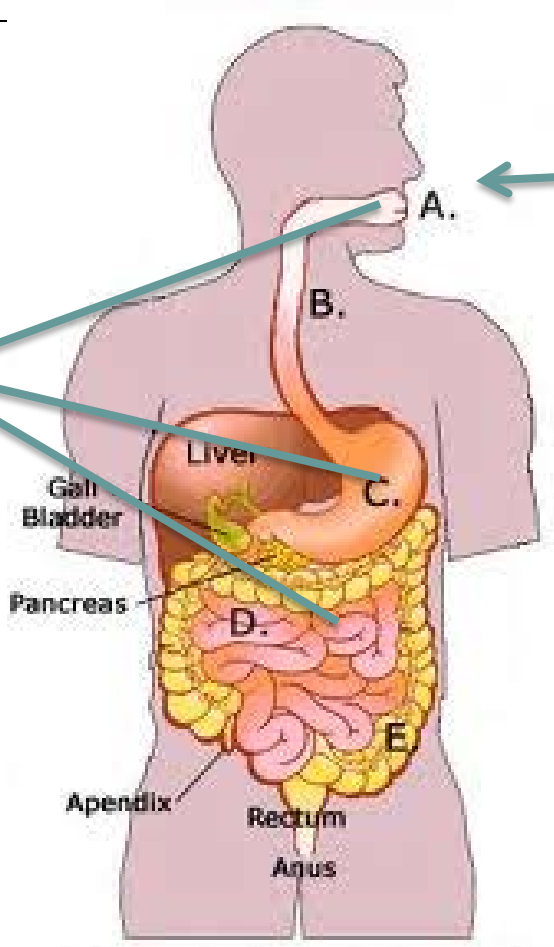
Metal substance external concentration

- Soil/Dust
- Water
- Food

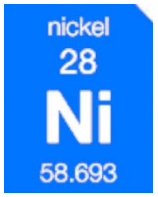
Systemically absorbed dose

Bioavailable RfD



Bioavailable exposure can account for differential absorption from various media!

Conclusions



- EPA Metals Framework is a good guidance document
- Other metal-specific guidance documents: HERAG
  - http://www.ebrc.de/industrial-chemicals-reach/projects-and-references/herag.php

- Consider bioavailability and bioaccessibility of metal ions from various chemical forms, metal-containing media, metal-containing particles, and via relevant routes of exposure

- For inhalation route and local respiratory effects, the use of dosimetric models with appropriate particle size data is critical to derive relevant equivalent human exposures

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THANK YOU FOR YOUR ATTENTION !

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