

Risk Assessment for Essential Metals: Considerations for “The Path Forward”

**Workshop on Health Risk
Assessment of Essential Metals
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Exposure:

Bioaccessibility/Bioavailability

- Further development of *in vitro* bioaccessibility models for essential metals
- *In vitro* models for intestinal absorption?
- Integration with dietary modifying factors – relate to population variability
- Integration with *in vivo* models
- Form in food often \neq form in soil, air, water

Use of New Technologies in Risk Assessment

- A Role for Omics?
 - Genomics
 - Proteomics (post-translational modifications?)
 - Metabolomics (esp. considering role of essential metals in redox chemistry)
- Use of computational biology
 - [See Toxicity Testing in the 21st Century (NAS, 2007)]

Use of New Technologies in Risk Assessment (*cont.*)

- Need to understand functional/toxicity pathways to appropriately interpret changes due to:
 - Deficiency states
 - Sufficiency states
 - RDA (basal)
 - RDA and above (normative)
 - Toxic states
- Identify concentration(s) for transitions from basal/normative to toxic state
- Need for phenotypic anchoring (and the most appropriate anchor – e.g. SOD inhibition vs. inhibition of Cu/Fe uptake)

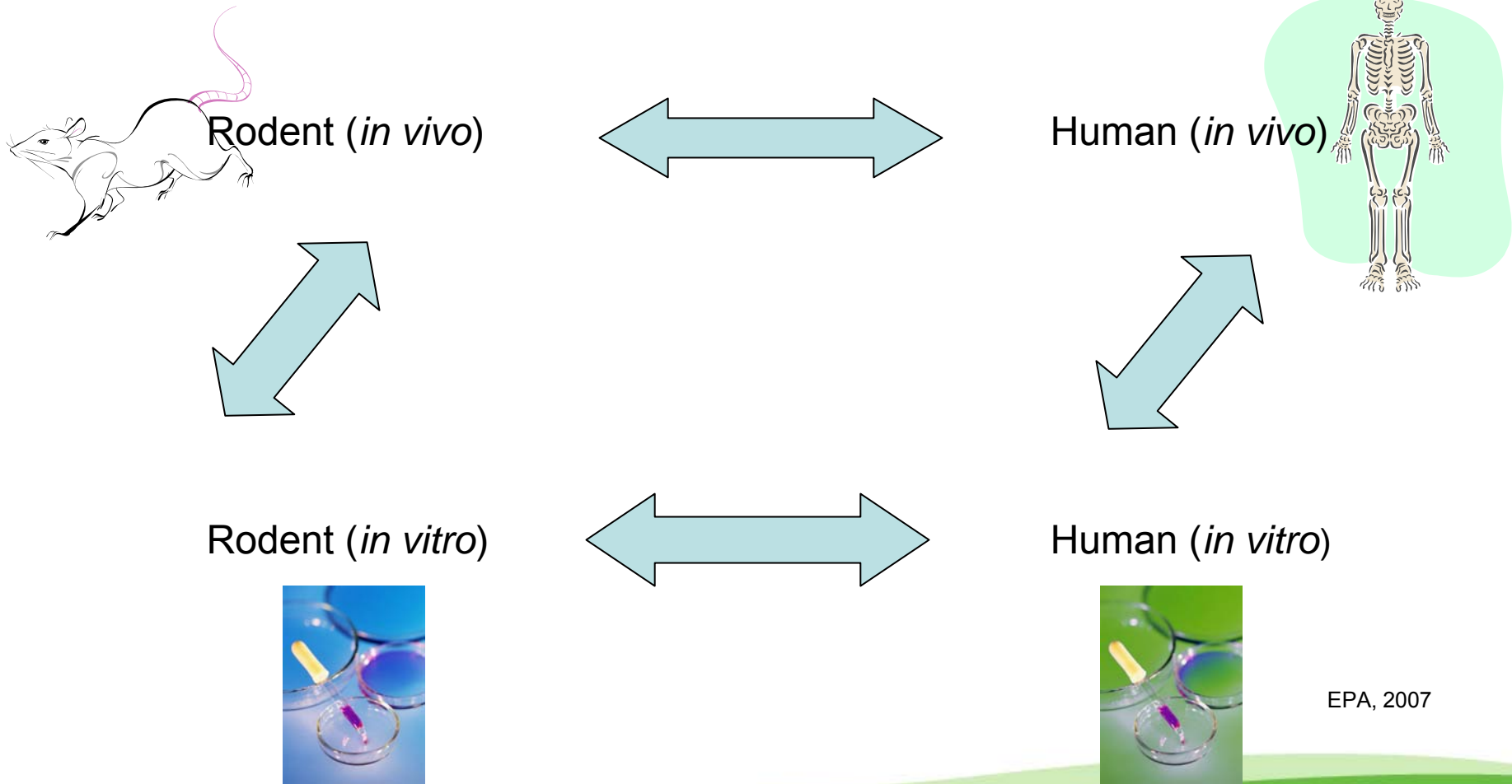
In Vitro Genomic Changes: An Example Using As₂S₃

	~Stress / adaptation		~Cell cycle control, DNA repair, relevance to carcinogenesis		~Apoptosis
	0.01 uM	0.1 uM	1.0 uM	10 uM	100 uM
Oxidative Stress	Trx Trx Reductase SOD1	AP-1	HO-1 GSR TPX-11		MT-1 MT-2 NRF-2
Inflammation	COX-2			IL-8	
Proteotoxicity	HSP-32		HSP-70		HSP-60 HSP-27
Proliferation	FGFR-4	Fos Jun	VEGF Myc P70 Erk		ERK-1 ERK-2 EGFR
DNA Repair	DDB2	Pol beta Ligase I	PARP-1	Liagase I	GADD153
Cell Cycle Control		P53	CDC25A CDC25B CDC25C	P21	
Apoptosis	P53 EGR-1 P105 P65	NF-kB P53	Casp3 Casp8 Casp9		SRC JNK JNK3

Clewell *et al.*, 2007.

Gene Expression: Increase Decrease

Relating Changes to Risk Assessment: Parallelogram Approach



EPA, 2007

Details, Details...

- Appropriate cell type
 - Primary vs. cell line
 - Particular challenge with essential metals – multiplicity of cellular targets – for essentiality and for toxicity.
 - Zn – homeostasis at level of GI tract in particular
 - Zn – toxicity – multiple targets, Cu-containing enzymes
- Time course – initial *in vivo* perturbation can be followed by re-establishment of homeostasis (e.g. SH-amino acid deficiency & metabolomic changes) – can this happen *in vitro*?
- Susceptible populations – what are appropriate models?
 - Essential dose can vary
 - Potentially toxic dose can vary, qualitatively and quantitatively
- Form of essential metal to test – species, bioavailability, *etc.*

Another Consideration for Risk Assessment

- Perturbations in toxicity pathways and identification of “transcriptional neutrality”
- “Transcriptional neutrality” not appropriate for essential metals
- It’s all about homeostasis and beyond