Computer-Aided Design of Nanomaterials with the Desired Bioactivity and Safety Profiles (T425.044)

Database compilation

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Research Objectives

- **Create, curate and maintain a specialized database incorporating various information on nanomaterials including their physical/chemical properties and associated biological data emerging from both ERC research teams and the scientific literature.**

- **Curated, searchable online database of manufactured nanoparticles including their physical chemical characteristics, *in vitro/in vivo* biological effects, and links to corresponding publications.**

- **Data resources needed for further modeling and analysis**

ESH Metrics and Impact

1. **Obtain a large integrated repository of the physical, chemical, and biological properties of manufactured nanoparticles.**

2. **Develop predictive computational models that correlate physical-chemical descriptors of MNPs with their toxic effects.**

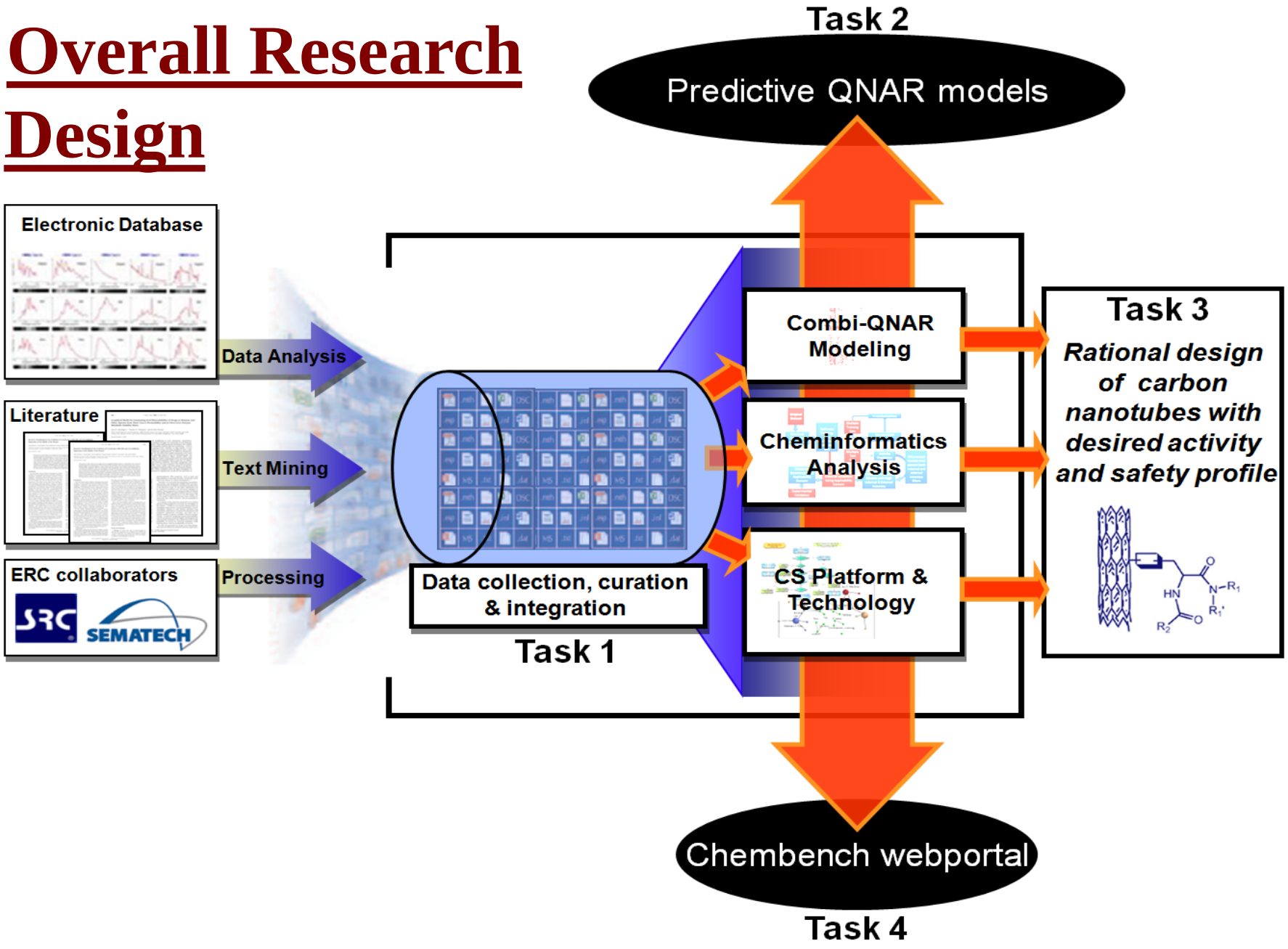
Impact: Utilize the knowledge gained through the analysis of the database for improved MNP experimental design and prioritized toxicity testing toward the manufacturing of safe nanomaterials.

Data depositories

Studies on MNP of different core structure, size, shape, and with various surface modifications have been reported but all published data are diverse, non-searchable, and spread among numerous sources of information.

- **Lack of centralized data repository**
- **Limits our capability to develop predictive tools to assess nanotoxicity in advance of manufacturing**
- **Severely limits the design of novel nanomaterials that are environmentally benign and safe for human exposure**

Overall Research Design

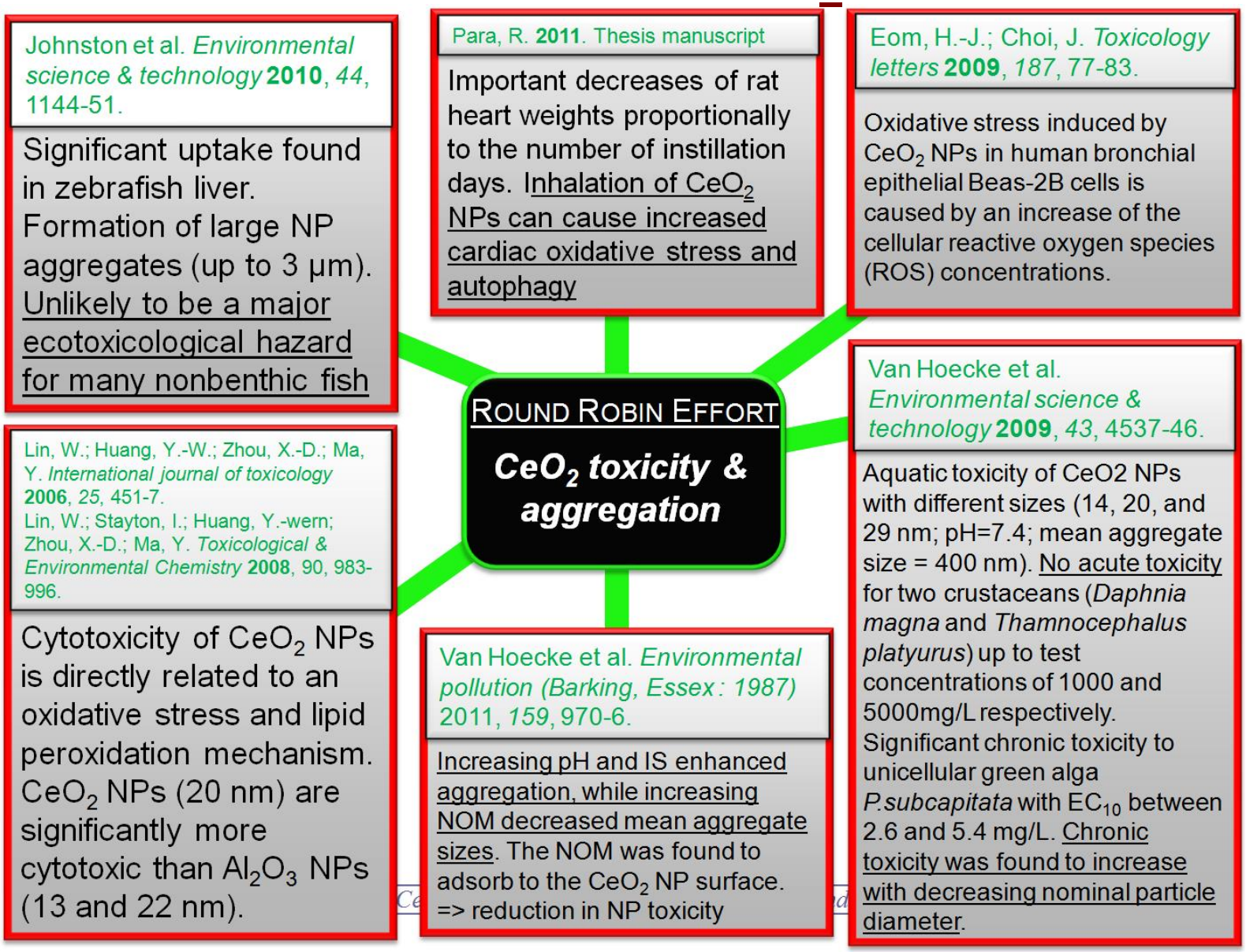


Where is the data? How to compile it? How reliable is it?

We are exploring three distinct ways of compiling and extracting experimental data:

1. **Manual searches in literature and internet resources;**
2. **Integration from electronic database and experimental collaborators;**
3. **Automatic literature searches using text-mining approaches.**

1 Manual search in literature and internet resources – Case Study: CeO_2



Experimental confirmation of literature-extracted sizes of CeO_2 nanoparticles in various medium

Johnston et al. *Environmental science & technology* 2010, *44*, 1144-51.

"Formation of large NP aggregates (up to 3 µm)"
"Aggregate formation was concentration-dependent and varied with the type of water used in the exposures."

Average particle size and SD of CeO_2 nanoparticles (20 µg/ml)

at 0 h.

Sample (CeO_2, 20µg/ml)	pH	Average	SD
H_2O	4.5	**123.9**	15.6
	6	**122**	15
	7	**1151.1**	450.3
H_2O with 0.5% v/v Dispex A40	8	**140**	13.8
DMEM, No FBS	7.4	**1547.1**	154.8
DMEM + 10% FBS	7.4	**454.9**	22.4

at 24 h.

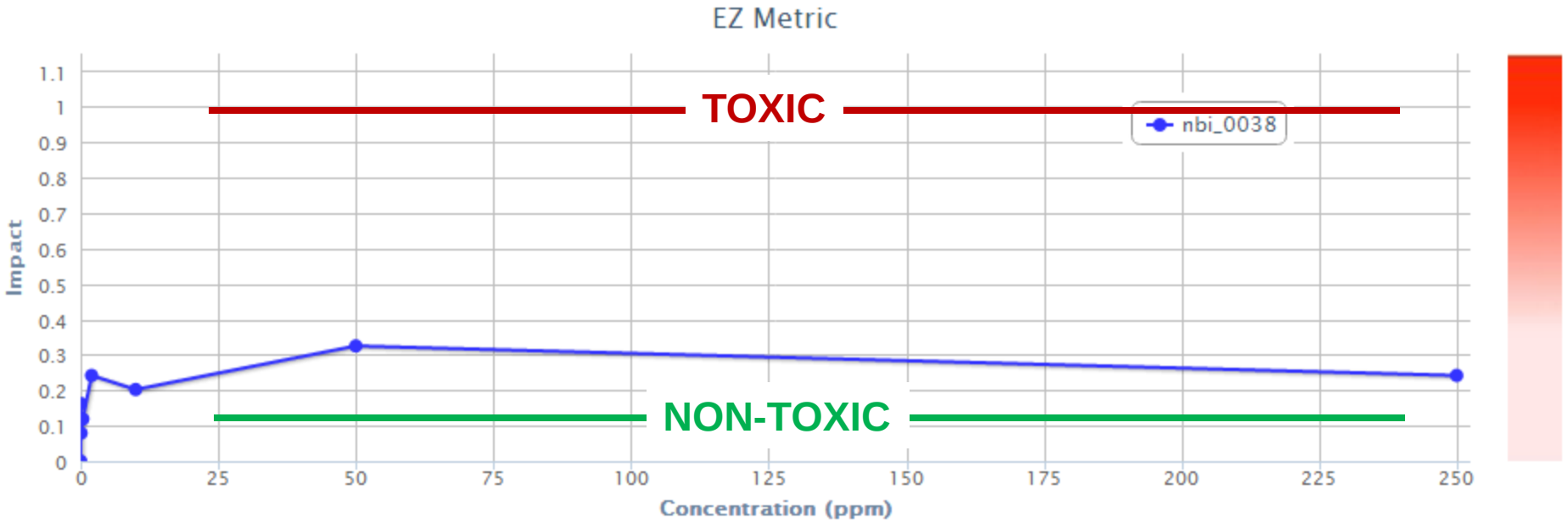
Sample (CeO_2, 20 µg/ml)	pH	Average	SD
H_2O	4.5	**144.1**	11.8
	6	**114.1**	3.1
	7	**3000**	0
H_2O with 0.5% v/v Dispex A40	8	**149.9**	26.2
DMEM, No FBS	7.4	**2964**	5.6
DMEM + 10% FBS	7.4	**475.3**	65.9

From CeO_2 Round Robin Report by Drs Tropsha and Mumper, UNC-CH, 2011.

2 *In vivo* bioprofile of CeO_2 nanoparticles measured in Embryonic Zebrafish

From the Nanomaterial-Biological Interactions Knowledgebase freely accessible at http://nbi.oregonstate.edu/

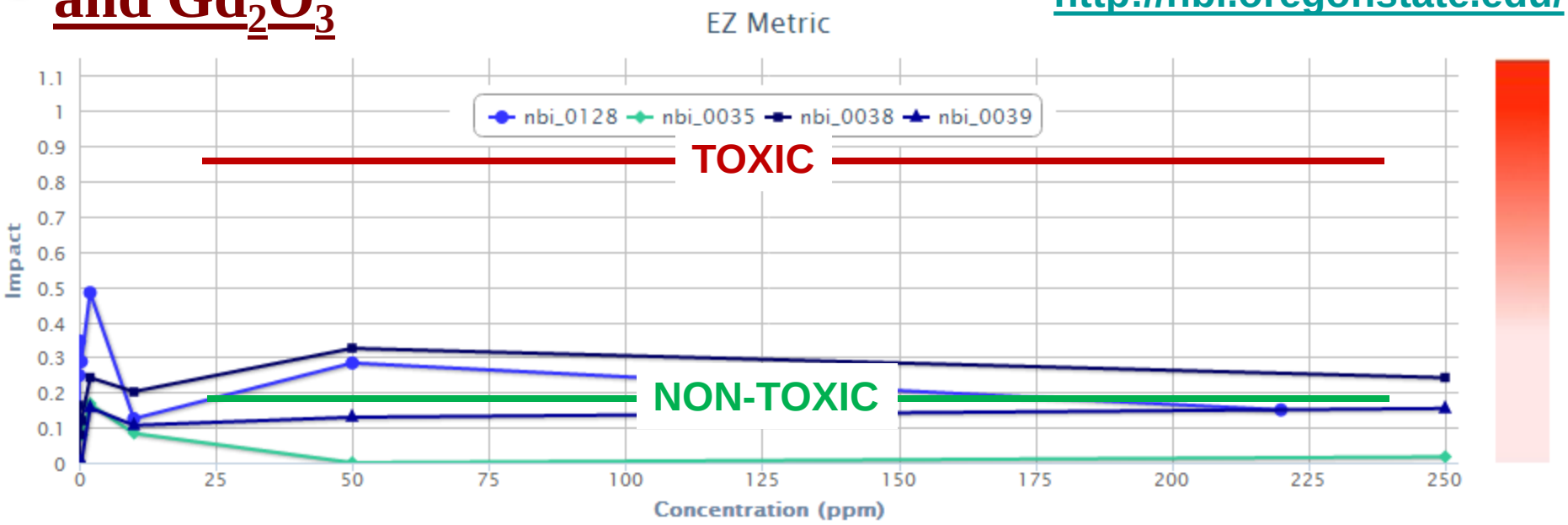
Evaluation of nanotoxicity in embryonic zebrafish screening-level assay



Nanomaterial							EZ Metric								
ID	Family	Core	Surface Chemistry	Shape	Size	Charge	Concentration								
nbi_0038	metal oxide	cerium oxide [CeO2]		spherical	0 - 25		control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm	Data
Average Values							0.00	0.16	0.08	0.12	0.24	0.20	0.33	0.24	View

2 Comparison of bioprofiles for Al_2O_3, CeO_2, Fe_2O_3 and Gd_2O_3

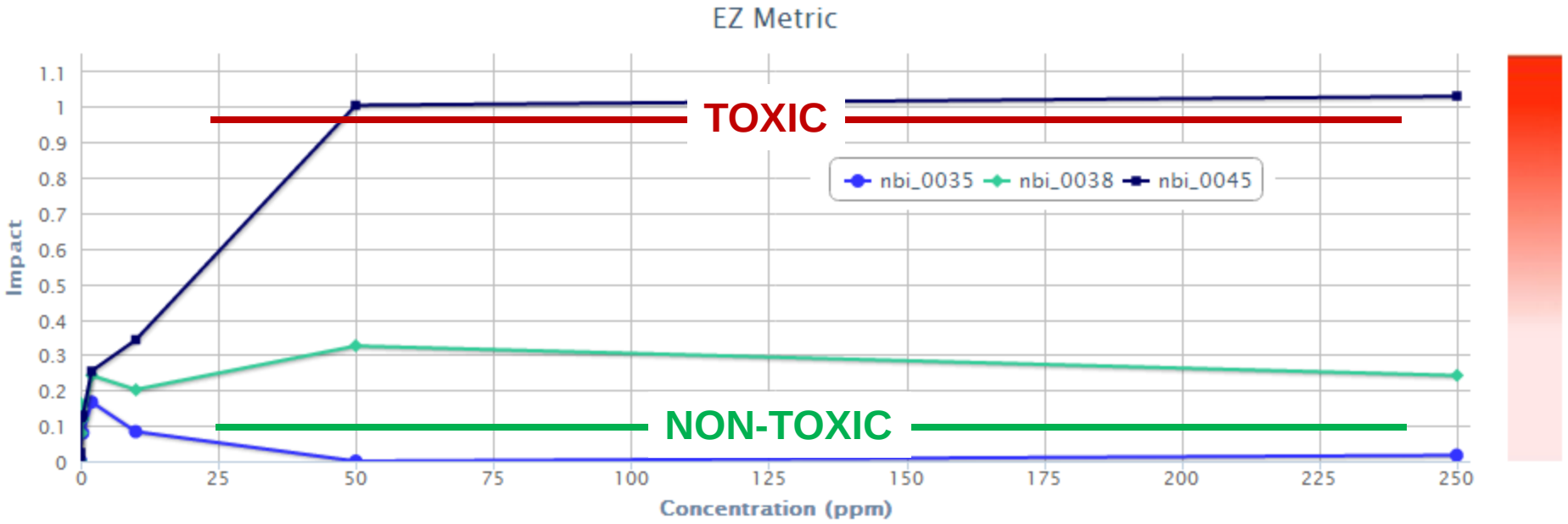
http://nbi.oregonstate.edu/



Nanomaterial							EZ Metric								
ID	Family	Core	Surface Chemistry	Shape	Size	Charge	Concentration								
nbi_0128	metal oxide	iron oxide [Fe2O3]			110	-	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	220 ppm	Data
Average Values							0.08	0.25	0.35	0.29	0.48	0.12	0.28	0.15	View
nbi_0035	metal oxide	aluminum oxide [Al2O3]		spherical	0 - 50		control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm	Data
Average Values							0.00	0.08	0.11	0.08	0.17	0.08	0.00	0.02	View
nbi_0038	metal oxide	cerium oxide [CeO2]		spherical	0 - 25		control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm	Data
Average Values							0.00	0.16	0.08	0.12	0.24	0.20	0.33	0.24	View
nbi_0039	metal oxide	gadolinium oxide [Gd2O3]		cylindrical	0 - 49		control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm	Data
Average Values							0.00	0.00	0.00	0.00	0.16	0.11	0.13	0.15	View

2 Comparison of bioprofiles for Al_2O_3, CeO_2, and Er_2O_3

http://nbi.oregonstate.edu/



Nanomaterial							EZ Metric								
ID	Family	Core	Surface Chemistry	Shape	Size	Charge	Concentration								
nbi_0035	metal oxide	aluminum oxide [Al2O3]		spherical	0 - 50		control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm	Data
Average Values							0.00	0.08	0.11	0.08	0.17	0.08	0.00	0.02	View
nbi_0038	metal oxide	cerium oxide [CeO2]		spherical	0 - 25		control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm	Data
Average Values							0.00	0.16	0.08	0.12	0.24	0.20	0.33	0.24	View
nbi_0045	metal oxide	erbium oxide [Er2O3]		spherical	0 - 49		control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm	Data
Average Values							0.02	0.00	0.12	0.13	0.25	0.34	1.00	1.03	View

Zebrafish toxicity profiles for metal oxides

(exp. data taken from http://nbi.oregonstate.edu/)

Core	Surface Chemistry	Size	Concentration							
			control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
silicon dioxide [SiO2];aluminum oxide [Al2O3]		0 - 49	0	0.04	0	0.04	0	0.12	0.18	0.36
zinc oxide [ZnO]	oleic acid	62	0.04	0.21	0.34	0.08	0.17	0.08	0.21	0.08
zinc oxide [ZnO]	oleic acid	26	0.04	0.22	0.29	0.08	0.25	0.33	0.42	0.46
zinc oxide [ZnO]		26	0.04	0.17	0.08	0.22	0.35	0.14	0.12	0.29
zinc oxide [ZnO]	para-nitrobenzoic ..	62	0.04	0	0.04	0.08	0.17	0.04	0.04	0.14
zinc oxide [ZnO]			0.04	0.17	0.33	0.21	0.17	0.12	0.27	0.29
zinc oxide [ZnO]		12.6 - 16.6	0.02	0.07	0.3	0.12	0.14	0.04	0.06	0.25
zinc oxide [ZnO]		18.3 - 48.9	0.08	0.16	0.02	0.24	0.12	0.04	0.2	0.22
zinc oxide [ZnO]		4 - 5	0	0.12	0.23	0.24	0.2	0.31	0.34	0.36
zinc oxide [ZnO]		8.7 - 11.7	0.08	0.25	0.22	0.04	0.11	0.36	0.17	0.25
zinc oxide [ZnO]		4.9	0	0.17	0.12	0.33	0.09	0.15	0.12	0.05
zinc oxide [ZnO]		3.9 - 5.5	0.08	0.12	0.21	0.25	0.25	0.38	0.33	0.08
iron oxide [Fe2O3]		110	0.08	0.25	0.35	0.29	0.48	0.12	0.28	0.15
zinc oxide [ZnO]		4	0.06	0	0	0.17	0.01	0	0.09	0.32
zinc oxide [ZnO]	ferric oxide	4	0.06	0.04	0	0	0	0.01	0.09	0.03
aluminum oxide [Al2O3]		0 - 50	0	0.08	0.11	0.08	0.17	0.08	0	0.02
titanium dioxide [TiO2]		20 - 40	0	0.04	0.05	0.1	0	0.07	0.17	0.17
zinc oxide [ZnO]	octanoic acid	62	0.04	0.16	0.2	0.29	0.17	0.48	0.29	0.33
zinc oxide [ZnO]	octanoic acid	26	0.04	0.17	0.24	0.12	0.27	0.12	0.38	0.29
zinc oxide [ZnO]	para-nitrobenzoic ..	26	0	0	0	0	0.04	0.2	0.05	0.09
zinc oxide [ZnO]	cyclohexane carbox.	62	0	0.22	0	0.12	0.29	0.29	0.25	0.29
zinc oxide [ZnO]	cyclohexane carbox.	26	0	0.14	0.04	0.08	0	0	0.01	0.14
zinc oxide [ZnO]	benzoic acid	62	0.08	0.29	0.16	0.25	0.08	0.29	0.17	0.2
yttrium oxide [Y2O3]		0 - 49	0	0.06	0.21	0.24	0.24	0.39	0.53	0.54
zirconium oxide [O2Zr]		0 - 99	0	0.1	0.14	0.1	0.16	0.1	0.06	0.28
Holmium oxide [Ho2O3]		0 - 49	0	0.12	0.26	0.26	0.29	0.28	0.56	0.97
cerium oxide [CeO2]		0 - 25	0	0.16	0.08	0.12	0.24	0.2	0.33	0.24
samarium oxide [Sm2O3]		0 - 49	0.04	0.12	0.12	0.18	0.18	0.42	0.91	0.96
gadolinium oxide [Gd2O3]		0 - 49	0	0	0	0	0.16	0.11	0.13	0.15
erbium oxide [Er2O3]		0 - 49	0.02	0	0.12	0.13	0.25	0.34	1	1.03

What descriptors/fingerprints are the most appropriate to differentiate MNPs with experimentally confirmed toxicity from non-toxic MNPs?

3 Chemotext platform for automatic text-mining

- **Built on top of the Medline annotation database containing over 19 million references to journal articles in life sciences;**

- **Records are indexed using NLM Medical Subject Headings (MeSH) exploited by Chemotext to rapidly query, mine, and extract relevant chemocentric information.**

- **Beta version is available at http://chembench-dev.mml.unc.edu:8082/**

Baker, J Biomed Inform, 2010, 43, 510-519

Fourches et al, Chem Research Tox, 2010, 23, 171-183

3 Compilation of assertions concerning the following properties of MNPs:

- Type **A** – Constitutional, structural, physical and chemical characteristics: *e.g.,* notes concerning aggregation, size distribution, solubility, etc.

- Type **B** – Protein targets or other biological receptors: *e.g.,* Cyclooxygenase 2, Superoxide Dismutase

- Type **C** – Reported biological effects at the cellular level: *e.g.,* apoptosis, oxidative stress, necrosis

- Type **D** – Reported biological effects at the whole tissue/organ/organism level: *e.g.,* pulmonary fibrosis, skin sensitization

As a pilot project, we have focused on two types of MNPs of industrial potential: cerium oxide and carbon nanotubes. We especially chose these MNPs because of the Round Robin's ongoing effort within the SRC research teams.

3 Most frequent biomedical terms associated with CeO_2 NPs found by Chemotext.

Term	Number of assertions
Particle Size	23
Oxidative Stress	20
Cell Survival	17
Lung	13
Macrophages	12
Cell Line	12
Apoptosis	10
Epithelial Cells	7
Time Factors	7
Cell Line, Tumor	6
Cell Proliferation	6
Inflammation	6
Liver	6
Oxidation-Reduction	6
Phagocytosis	6
Superoxide Dismutase	6
Surface Properties	6
Cytokines	6

Manual and automatic text mining approaches led to similar observations concerning CeO_2 induced effects reported in literature.

➡ **Chemotext as a rapid and efficient approach to retrieve valuable nanomaterial-related information**

➡ **New Round Robin efforts must take this information into account to select the appropriate biological assays/experimental protocols to test CeO_2 NPs.**

Distribution and evolution of the CeO_2 retrieved assertions

Several time-dependent trends in the evolution of a given assertion

CeO2 assertions	2005	2006	2007	2008	2009	2010	2011	2012
Particle Size	1		1	1	2	5	7	6
Oxidative Stress		2	2	2	1	1	9	3
Cell Survival		2	1	1	1	4	5	3
Macrophages			2	2	2		4	2
Cell Line			1	3	2	3		3
Apoptosis	1			2		2	3	2
Lung		1		1		2	4	3
Epithelial Cells				2	1	3		1
Time Factors				1	1	1	1	1
Cell Line, Tumor		2				2	2	
Cell Proliferation						4	2	
Inflammation					2		3	1
Liver							2	3
Oxidation-Reduction		1		1	1	1	2	
Phagocytosis							2	4
Superoxide Dismutase				1	1	2	2	1
Surface Properties				1		3	2	
Cytokines					1	1	2	1

Main Parameter

Main Effects

Main Organ

Biological processes

Direct access to major papers linking CeO_2 with OXIDATIVE STRESS

Year of the publication	Title of the publication	Pubmed ID
2006	Cerium and yttrium oxide nanoparticles are neuroprotective.	16480682
2006	**Toxicity of cerium oxide nanoparticles in human lung cancer cells.**	17132603
2007	Cardioprotective effects of cerium oxide nanoparticles in a transgenic murine model of cardiomyopathy.	17207782
2007	Novel synthesis of cerium oxide nanoparticles for free radical scavenging.	17716177
2008	**Oxidative stress induced by cerium oxide nanoparticles in cultured BEAS-2B cells.**	18243471
2008	Comparison of the mechanism of toxicity of zinc oxide and cerium oxide nanoparticles based on dissolution and oxidative stress properties.	19206459
2009	**Oxidative stress of CeO2 nanoparticles via p38-Nrf-2 signaling pathway in human bronchial epithelial cell, Beas-2B.**	19429248
2010	Brain distribution and toxicological evaluation of a systemically delivered engineered nanoscale ceria.	20457660
2011	**Oxidative stress studies of six TiO2,, and two CeO2,, nanomaterials: immuno-spin trapping results with DNA.**	21142840
2011	**Cerium oxide nanoparticles: a promise for applications in therapy.**	21275265
2011	The protective effects of cerium oxide nanoparticles against hepatic oxidative damage induced by monocrotaline.	21289991
2011	**Nano-CeO2 exhibits adverse effects at environmental relevant concentrations.**	21428445
2011	Cerium oxide nanoparticles inhibit oxidative stress and nuclear factor- activation in H9c2 cardiomyocytes exposed to cigarette smoke extract.	21464334
2011	**Acute inhalation toxicity of cerium oxide nanoparticles in rats.**	21624445
2011	**Cellular responses induced by cerium oxide nanoparticles: induction of intracellular calcium level and oxidative stress on culture cells.**	21693544
2011	Neuroprotective mechanisms of cerium oxide nanoparticles in a mouse hippocampal brain slice model of ischemia.	21704154
2011	**Inorganic nanoparticles enhance the production of reactive oxygen species (ROS) during the autoxidation of L-3,4-dihydroxyphenylalanine (L-dopa).**	21737115
2012	**Distribution, elimination, and biopersistence to 90 days of a systemically introduced 30 nm ceria-engineered nanomaterial in rats.**	22367688
2012	**Alteration of hepatic structure and oxidative stress induced by intravenous nanoceria.**	22373796
2012	Improvement of isolated rat pancreatic islets function by combination of cerium oxide nanoparticles/sodium selenite through reduction of oxidative stress.	22409398

Industrial Interactions and Technology Transfer

To integrate more experimental MNP related data, we are collaborating with the following research teams:

- **RTI – Kim Guzan (RTP)**
  Integration and Analysis of their Internal Database (~100 MNPs)

- **Nano Working Group (Nathan Baker and Stacey Harper)**
  Integration and Analysis of MNP - Zebrafish dataset

- **EPA – Amy Wang**
  Integration and Modeling of their NP database being part of the Toxcast program (~80 NPs fully characterized and tested in both *in vitro* cell-based assays and *in invo*)

Future Plans

For the first year, our main goal was to explore what type of information and relationships are already present in the literature for key MNPs

Next Year Plans

- **Fully integrate all data sources in one single repository (ongoing process);**
- **Analyze the consistency and reliability of experimental data for each type of MNPs;**
- **Extract relevant subsets of MNPs tested in the same assay and build predictive QNAR models.**

Long-Term Plans

- **Deployment of the database to the overall community via our Chembench webportal (http://chembench.mml.unc.edu)**

Publications and Presentations

- **SOT 2013 Conference - presentation entitled "Quantitative Nanostructure-Activity Relationships"**

- **MRS 2012 Conference – presentation entitled "Rational Design of (Nano)materials with the Desired Biological Properties Using Quantitative Structure-property Relationships (QSPR) Modeling"**

- **Alexander Tropsha, Denis Fourches. Quantitative Nanostructure-Activity Relationships (QNAR) modeling: Applications to Rational Design of Nanomaterials with the Desired Bioactivity Profile. SRC Metrology Webinar Series, Jan. 20, 2012.**

- **Fourches D, Pu D, Tropsha A. Exploring quantitative nanostructure-activity relationships (QNAR) modeling as a tool for predicting biological effects of manufactured nanoparticles. Comb Chem High Throughput Screen. 2011, 14(3):217-25**