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

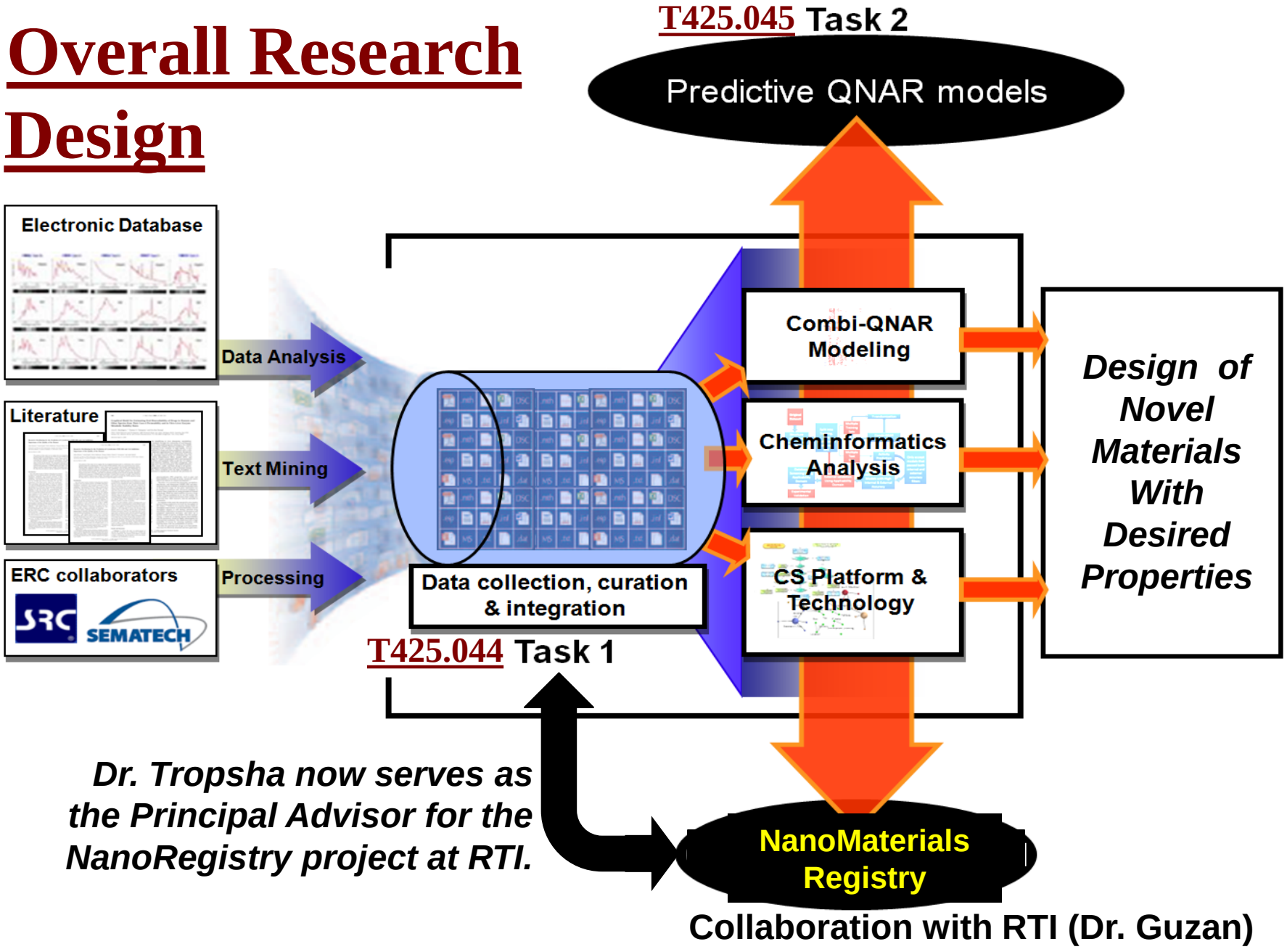
*Database compilation/integration

*Aquatic Toxicity

PIs:

- **Alexander Tropsha, PhD (University of North Carolina at Chapel Hill)**
- **Denis Fourches, PhD (University of North Carolina at Chapel Hill)**

Overall Research Design



Research Objectives

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

- **Curated, searchable online database of manufactured nanomaterials 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 experimental design and prioritized toxicity testing toward the manufacturing of safe nanomaterials.

FEDERAL NANOTECHNOLOGY INITIATIVE

The NNI Coordinates R&D in nanoscale science, engineering, and technology

NNI — National Nanotechnology Initiative

NKI — Nanotechnology Knowledge Infrastructure
Thrust 4: Digital Information Infrastructure

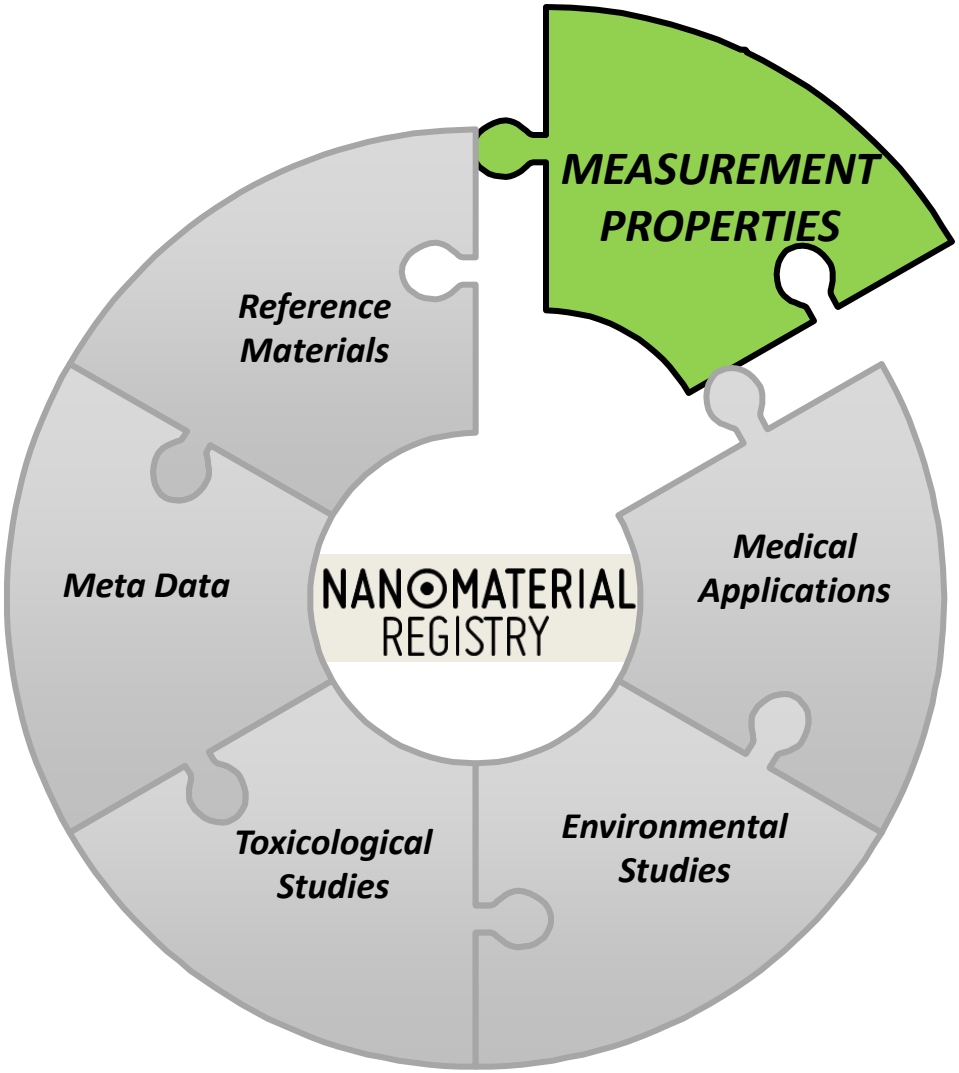
NIH — Nanomaterial Registry Project
www.nanomaterialregistry.org

FEDERAL AGENCIES
- **DoD**
- **DOE**
- **EPA**
- **FDA**
- **NASA**
- **NIH**
- **NIOSH**
- **NIST**
- **NSF**
- **OSHA**
- **…**

…cyber-toolbox, and data infrastructure that will shorten the time from research to new product development..

Adapted from Dr. Kim Guzan (RTI International)

MINIMAL INFORMATION CHARACTERIZATION DATA



NANOMATERIALREGISTRY

- Particle Size
- Size distribution
- Surface area
- Shape
- Composition
- Aggregation/ Agglomeration state
- Purity
- Surface chemistry
- Surface charge
- Surface reactivity
- Solubility
- Stability

PCC Data — *12 Physical and Chemical Characteristics*

Protocal & Parameters — *Information about instrumentation settings*

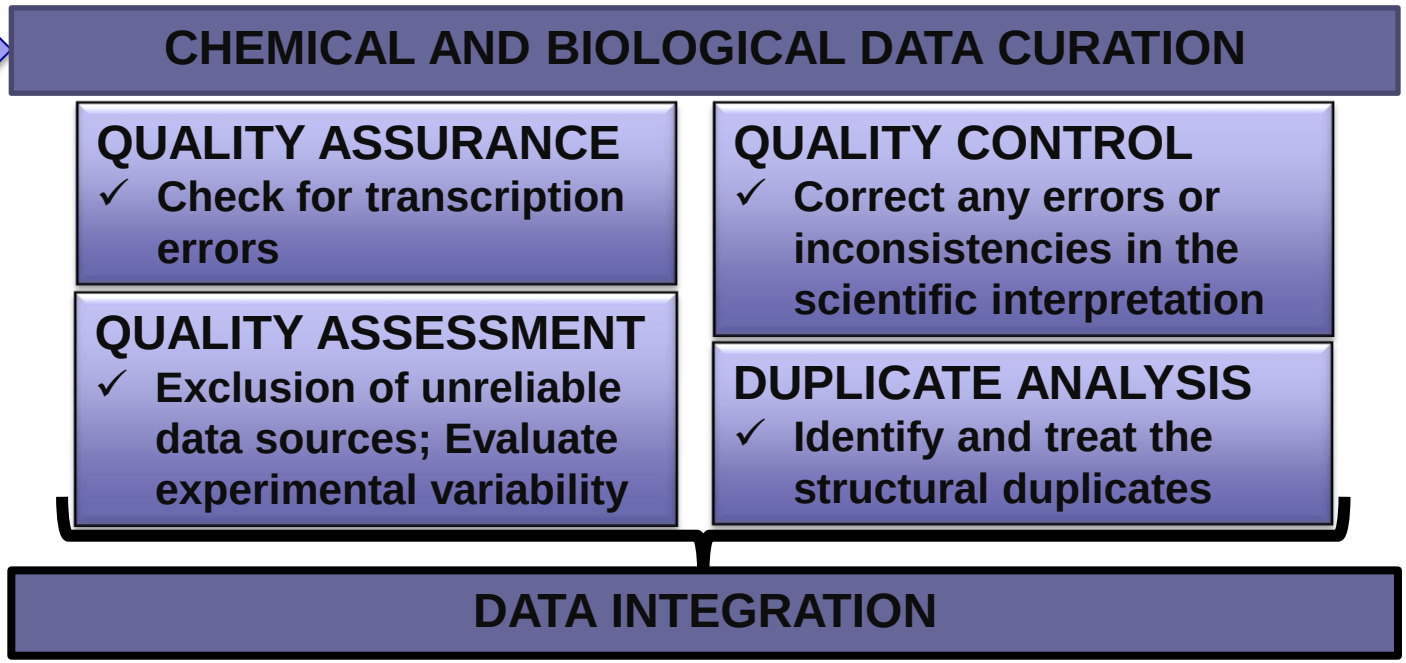
Best Practice Questions — *Meta data about measurement technique*

www.nanomaterialregistry.org

Adapted from Dr. Kim Guzan (RTI International) slide

Data Compilation/Curation/Integration

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



Data curation is critical to achieve high quality databases and enable modeling studies

ChemBark

News, Analysis, and Commentary for the World of Chemistry & Chemical Research

« Hacks for Septa

Organometallics Responds to the Dorta Situation »

A Disturbing Note in a Recent SI File

August 6th, 2013

A recently published ASAP article in the journal *Organometallics* is sure to raise some eyebrows in the chemical community. While the paper itself is a straightforward study of palladium and platinum bis-sulfoxide complexes, page 12 of the corresponding Supporting Information file contains what appears to be an editorial note that was inadvertently left in the published document:

> Emma, please insert NMR data here! where are they? and for this compound, just make up an elemental analysis…

ChemBark

Investigates

This statement goes beyond a simple embarrassing failure to properly edit the manuscript, as it appears the first author is being instructed to fabricate data. Elemental analyses would be very easy to fabricate, and long-time readers of this blog will recall how fake elemental analyses were pivotal to Bengu Sezen's campaign of fraud in the work she published from 2002 to 2005 out of Dalibor Sames' lab at Columbia.

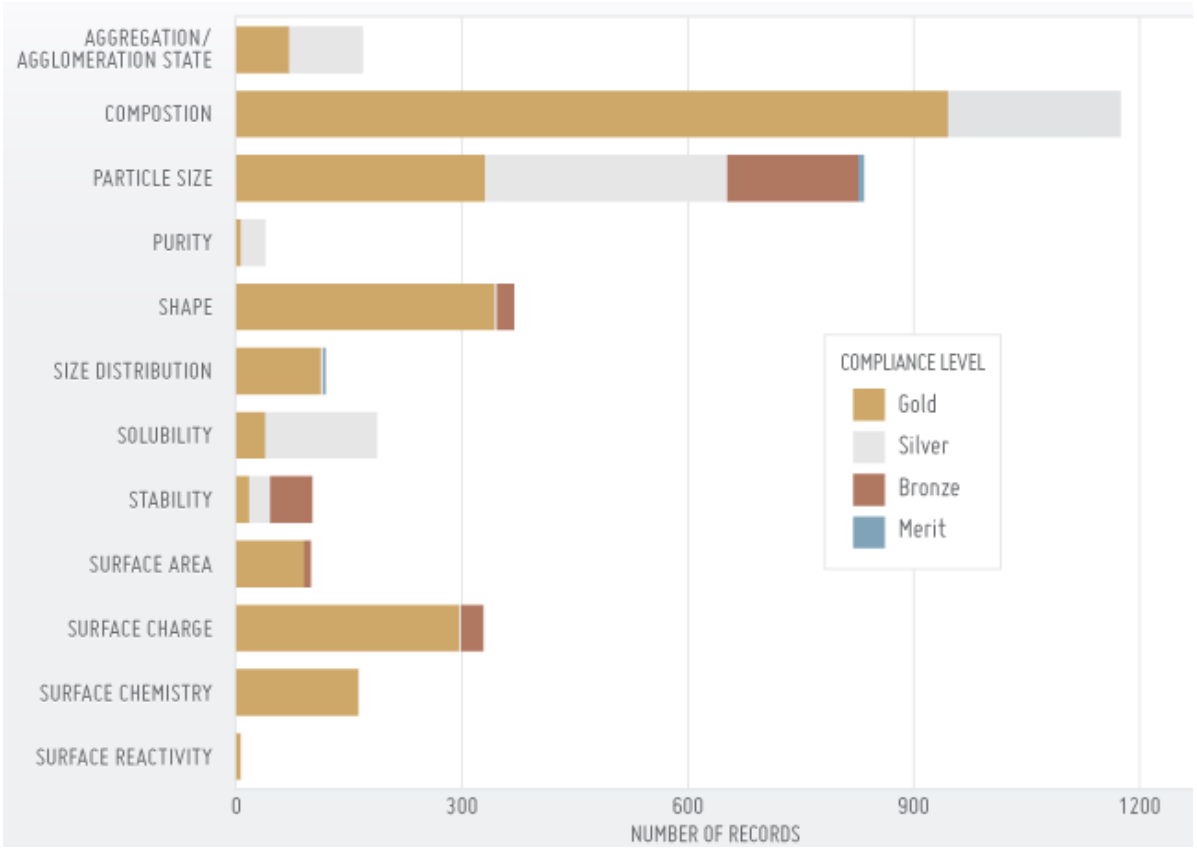
The compound labeled **14** (an acac complex) in the main paper does not appear to correspond to compound **14** in the SI. In fact, the bridged-dichloride compound appears to be listed an as unlabeled intermediate in Scheme 5, which should raise more eyebrows. Did the authors unlist the compound in order to avoid having to provide robust characterization for it?

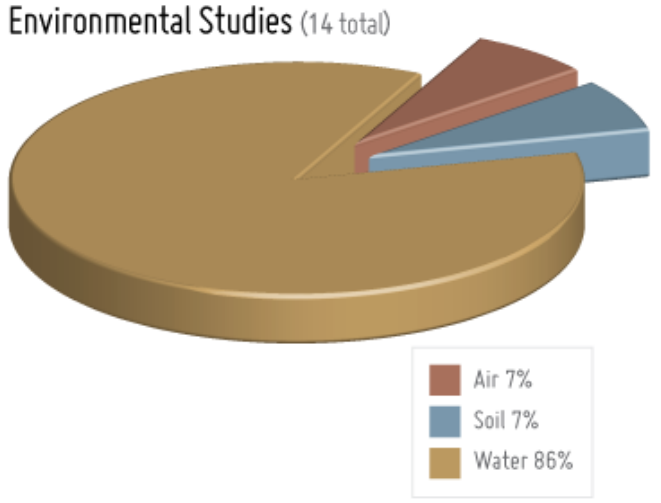
ChemBark is contacting the corresponding author for comment, and his response will be posted in full when we receive it.

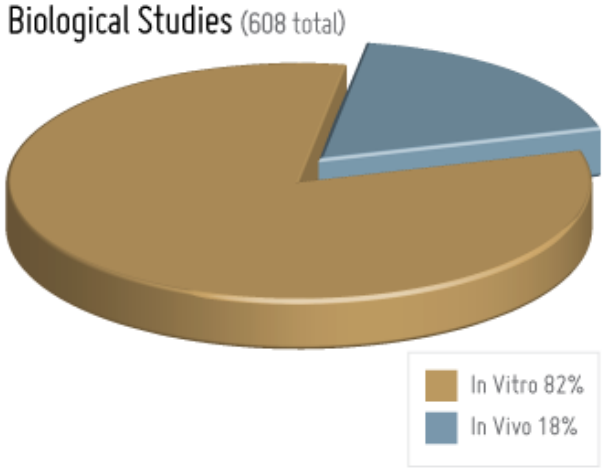
NanoRegistry - Contents

1284 Nanomaterials as of 10/31/2013

www.nanomaterialregistry.org





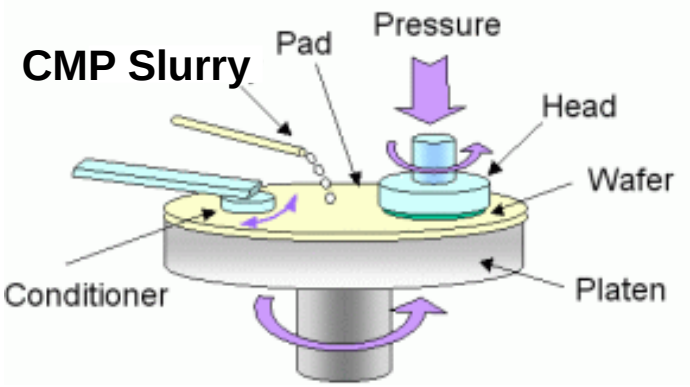


Data extraction using automated text mining: Chemotext platform *(Baker, J Biomed Inform, 2010, 43, 510-519)*

- **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.**
- **Text-mined chemical assertions can be used for developing predictive computational models.**
  Fourches et al., Chem Research Tox, 2010, 23, 171-183
- **Text-mined chemical assertions on nanomaterials can be used for:**
  - Enriching the database with more entries;
  - Helping the curation process with fast literature verifications;
  - Fast browsing of available literature data for a given material.

Evaluating the Toxicity of Chemical Mechanical Planarization Slurries

Alumina, silica, and ceria MNPs are used in semiconductor device fabrication during the CMP procedure to polish the surface of silicon wafers. They form stable suspensions (slurries) of abrasive nanomaterials dispersed in water with other chemicals.



Credit: www.agc.com

Importance of evaluating the toxicity for MNPs and organic compounds present in slurries

Most Important Endpoints

-**Skin irritation, skin sensitization, eye irritation** *[workplace exposure]*

- **Aquatic Toxicity, soil adsorption** *[environmental release]*

Organic Compounds present in various advanced CMP slurries

Role	Additives	Processes
Surfactants	Fluorinated carboxylic acids [4], Polyacrylic acids [20], carboxylic acids [44], quartenary ammonium salts (CTAB) [20], Polyvinyl alcohols (Triton)	STI, CuCMP
Inhibitors	Benzotriazole [14], hydrogen phthalate salts [4, 44]	CuCMP, WCMP, STI
Complexing Agents	hydroxylamines [13], ammonium hydroxlate [14], citric acid [14], lactic acid [14], tartaric acid [14], succinic acid [14], amino acids [14], acetic acid [15], EDTA [20]	CuCMP
Oxidizers	Oxalic acid [12], peroxides [14]	CuCMP
Microemulsions	Iso-propyl alcohol [18], glycerol [44]	STI, WCMP
Catalysts	Organic iron compounds [45]	WCMP

From Chemical Mechanical Planarization of Semiconductor Materials. M.R. Oliver. 2004, Springer, ISBN-10: 3540431810.

Conventional models for predicting the endpoints of interest: QSAR Model of Skin Sensitization *(Alves et al, EHP, 2014, Under Review)*

- End point: murine local lymph node assay (LLNA)
- Dataset (extracted from the ICCVAM report of LLNA): Following chemical data curation, 254 compounds retained for QSAR modeling (2D chemical descriptors and Random Forests):
  - **127 sensitizers and 127 non-sensitizers.**
  - **Consensus model (82% coverage): 79% CCR (*5-fold cross val.*)**

	Sensitivity	Specificity	CCR	Coverage
Model 1 - SiRMS	0.83	0.83	0.83	0.58
Model 2 - SiRMS no AD*	0.69	0.73	0.71	1.00
Model 3 - Dragon	0.84	0.87	0.85	0.52
Model 4 - Dragon no AD*	0.70	0.81	0.76	1.00
Model 5 - Consensus	0.79	0.85	0.82	0.70
Model 6 - Consensus no AD*	0.74	0.83	0.79	0.82
Model 7 - Consensus Rigor	0.91	0.85	0.88	0.39

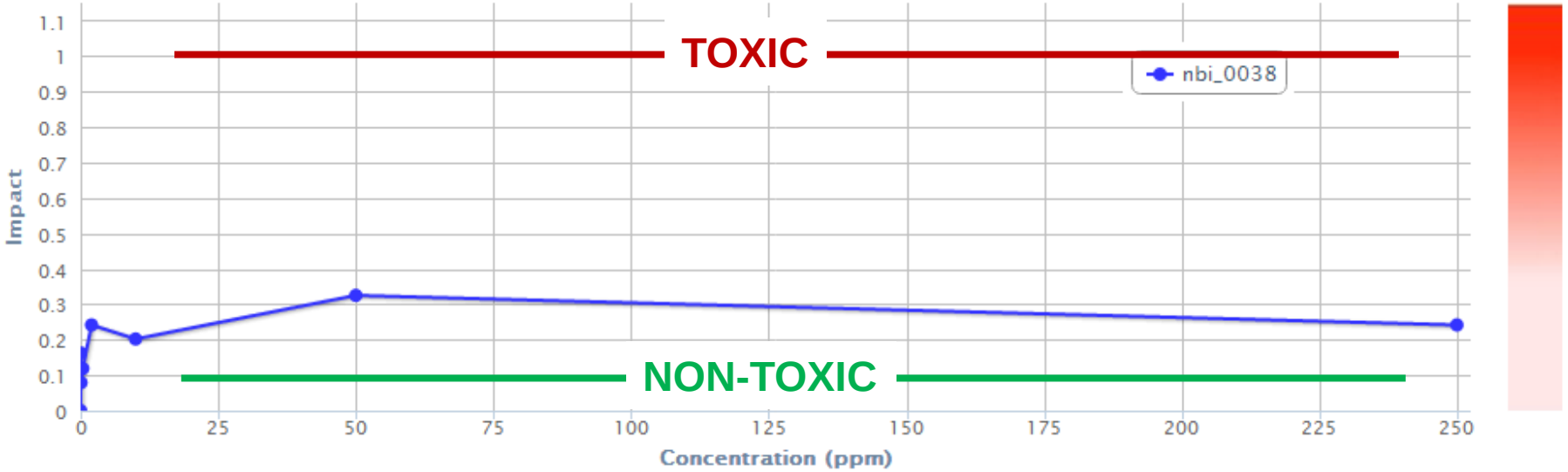
*Applicability Domain was not considered in these models.

These models were shown to higher external accuracy than OECD QSAR Toolbox when benchmarked on an external set of 153 compounds.

AQUATIC TOXICITY
In vivo bioprofile of CeO_2 nanoparticles measured in Embryonic Zebrafish

From the Nanomaterial-Biological Interactions Knowledgebase freely accessible at http://nbi.oregonstate.edu/ and **http://www.nanomaterialregistry.org**

Evaluation of nanotoxicity in embryonic zebrafish screening-level assay

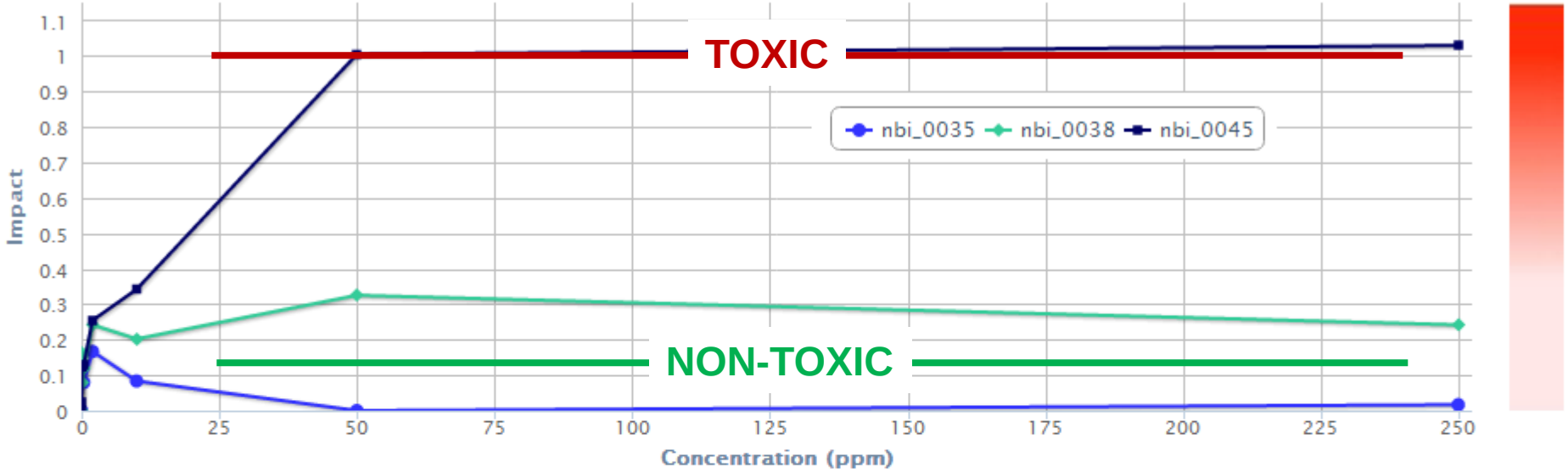


Nanomaterial							EZ Metric								
ID	Family	Core	Surface Chemistry	Shape	Size	Charge	Concentration								
nbi_0038	metal oxide	cerium oxide [CeO2]		spherical	0 - 25		control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm	Data
Average Values							0.00	0.16	0.08	0.12	0.24	0.20	0.33	0.24	View

AQUATIC TOXICITY

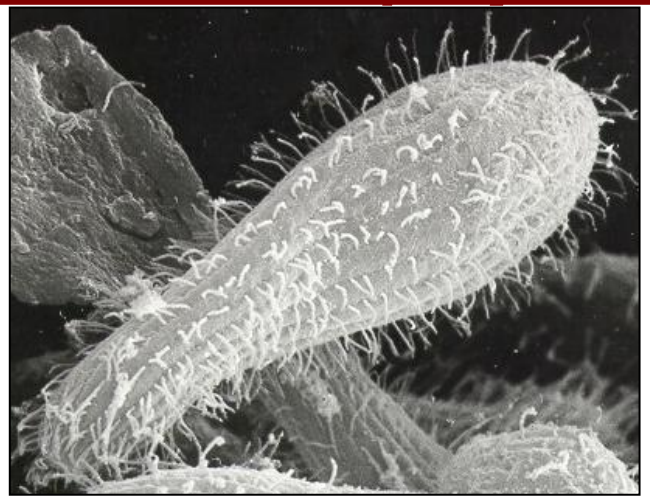
Comparison of bioprofiles for Al_2O_3, CeO_2, and Er_2O_3

Evaluation of nanotoxicity in embryonic zebrafish screening-level assay



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

Conventional models for predicting the endpoints of interest: QSAR Model of Aquatic Toxicity

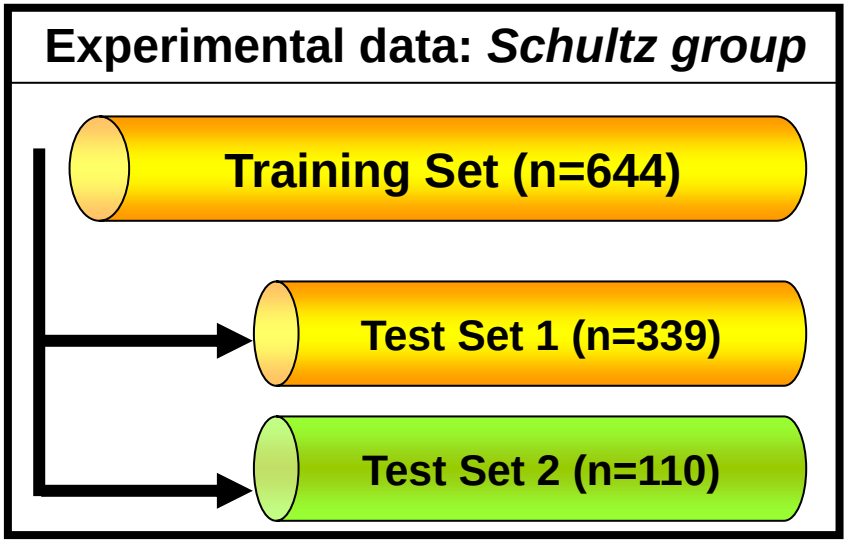


Tetrahymena Pyriformis

- Non-pathogenic ciliate protozoa.
- Common in fresh water.
- Used as model organisms in biomedical researches on aquatic toxicity (short generation time and inexpensive to be grown).

The 50% growth inhibition concentration, $IGC_{50,}$ was measured.

Zhu, Tropsha, Fourches et al., JCIM, 2008, 48 (4), 766–784.

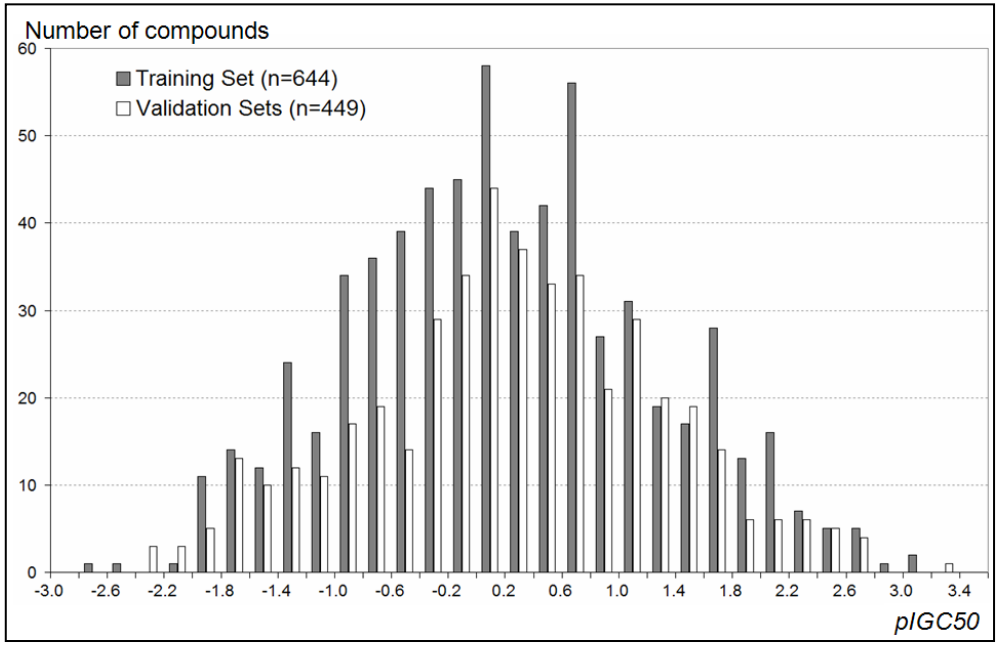


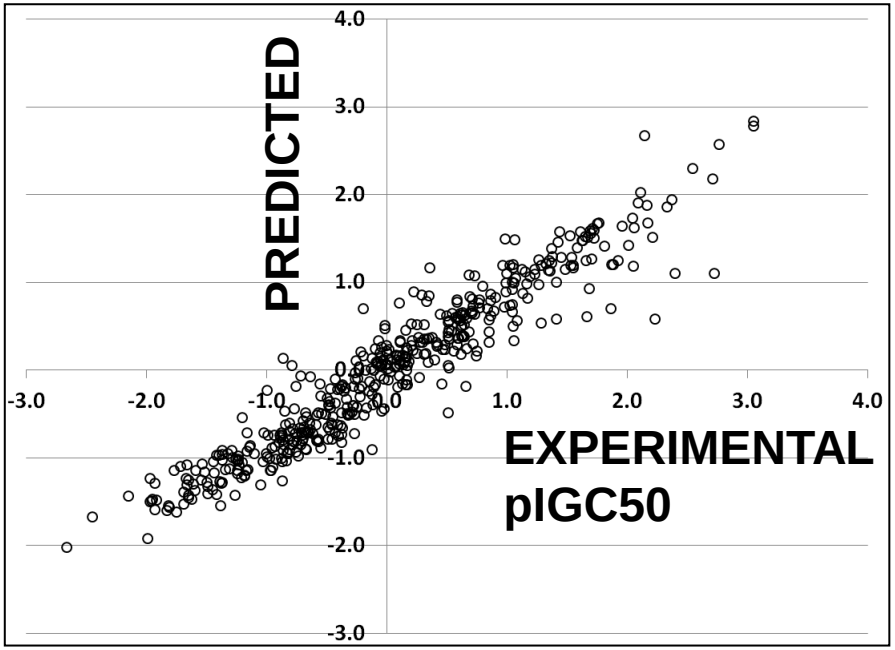
Modeling: *6 collaborating teams*

- University of North Carolina (UNC)
- Louis Pasteur University (ULP)
- University of Insubria (UI)
- University of Kalmar (UK)
- Virtual Computational Chemistry Laboratory (VCCLAB)
- University of British Columbia (UBC)

15 QSAR models

AQUATIC TOXICITY for organic compounds





Consensus Model	Training Set (n=644)			1st Evaluation Set (n=339)			2nd Evaluation Set (n=110)		
	R^2_{abs}	MAE	Coverage (%)	R^2_{abs}	MAE	Coverage (%)	R^2_{abs}	MAE	Coverage (%)
	0.92	0.22	**100**	0.86	0.28	**99.7**	0.70	0.34	**98.2**

Our QSAR model can be used as a reliable computational predictor of aquatic toxicity and is available at http://chembench.mml.unc.edu

Zhu, Tropsha, Fourches et al., JCIM, 2008, 48 (4), 766–784.

Evaluating the Toxicity of Chemical Mechanical Planarization Slurries

- Literature data suggest low skin penetration for diverse nanomaterials, but most studies concern MNPs utilized in sunscreens (TiO2, ZnO) …
  Monteiro-Riviere and Larese Filon. Effects of Engineered Nanomaterials on Skin. In Adverse Effects of Engineered Nanomaterials (Eds. B Fadeel, A. Pietroiusti, and A Shvedova), Elsevier, NY, Chapter 11, 185- 207, 2012.

- Literature data shows significant inter-species variations for lethal doses observed when testing a given MNP →

- SRC Round Robin efforts are revealing the complexity of slurries' chemical mixtures:
  -What are the most relevant *in vitro* and *in vivo* assays to evaluate their overall toxicity profile?
  -What are the best ways to use literature data when analyzing individual chemical components of slurries?
  -MNPs/chemicals synergistic toxicity?

NANO-COMPOUND	TEST SPECIES AND MEDIUM	LETHALITY	REFERENCE
TiO_2:			
<20 nm	*D.magna*	48 h LC_{50} = 143 ppm	Zhu *et al.*, 2009
25-30 nm	*D magna*	48 h LC_{50} = 5.5 ppm	Lovern and Klaper, 2006
	D.pulex	48 h LC_{50}> 10 ppm	Griffitt *et al.*, 2008
	C.dubia	48 h LC_{50}> 10 ppm	
	C.elegans	24 h LC_{50} = 80 ppm	Wang *et al.*, 2009
	P.scaber	14 d NOEC >1000 ppm	Drobne *et al.*, 2009
Al_2O_3 (60 nm)	*C.elegans*	24 h LC_{50} = 82 ppm	Wang *et al.*, 2009
Ag oxide (20-30 nm)	*D.magna*	48 h LC_{50} = 0.04 ppm	Griffitt *et al.*, 2008
	D.pulex	48 h LC_{50} = 0.067 ppm	
	C.dubia		
Al oxide: 20-30 nm; or 51 nm	*D.magna*	48 h LC_{50}> 162 ppm	Zhu *et al.*, 2009
	D.pulex	48 h LC_{50}> 10 ppm	Velzeboer *et al.*, 2008; Griffitt *et al.*, 2008
	C.dubia	48 h LC_{50} = 3.99 ppm	
Co oxide (10-20 nm)	*D.pulex*	48 h LC_{50}> 10 ppm	Griffitt *et al.*, 2008
	C.dubia	48 h LC_{50} = 1.67 ppm	
CuO:	*D.magna*	48 h LC_{50} = 3.2 ppm	Heinlaan *et al.*, 2008
30 nm, or	*T. platyurus*	48 h LC_{50} = 2.1 ppm	
15-45 nm	*D.pulex*	48 h LC_{50} = 0.06 ppm	Griffitt *et al.*, 2008
	C.dubia	48 h LC_{50} = 0.419 ppm	
Ni oxide (5-20 nm)	*D.pulex*	48 h LC_{50} = .89 ppm	Griffitt *et al.*, 2008
	C.dubia	48 h LC_{50} = 0.674 ppm	
SiO_2 (205>4,700 nm)	*D.magna*	48 h, LC_{70} = 10 ppm	Adams *et al.*, 2006
ZnO:			
20 nm	*D.magna*	48 h LC_{50} = 1.5 ppm	Zhu *et al.*, 2009
50-70 nm	*D.magna*	48 h LC_{50} = 3.2 ppm	Heinlaan *et al.*, 2008
	T. platyurus	48 h LC_{50} = 0.18ppm	
480>4,000 nm	*D. magna*	48 h LC_{73} = 0.2 ppm	Adams *et al.*, 2006
	C.elegans	24 h LC_{50} = 2.3 ppm	Wang *et al.*, 2009
$CuZnFe_2O_3$/Indium tin oxide/Ho_2O_3	*T. platyurus*	48h, LC_{50} = 0.1-1.0 ppm	Blaise *et al.*, 2008
	H. attenuata	96 h, EC_{50} = 10-100 ppm	
$NiZnFe_2O_3/O_3Sm_2$ / Er_2O_3	*T. platyurus*	48h, LC_{50} = 1-10 ppm	Blaise *et al.*, 2008
$SrFe_{12}O_{19}/TiO_2/Fe_2O_3$	*T. platyurus*	48h, LC_{50} = 10-100 ppm	Blaise *et al.*, 2008

Cattaneo et al., 2009, ISJ, 6, 78-97

Deliverables

- **Guidelines and protocols for the NanoMaterials Registry for data curation and features for querying and mining its internal database;**
- **Compilation of nanomaterials' aquatic toxicity data (*in vitro* and *in vivo*) freely available in the literature;**
- **QSAR models of aquatic toxicity for organic molecules;**
- **QSAR models of skin sensitization and skin permeability for organic molecules.**

Future Plans

- **Fully integrate all chemical and biological data sources in the NanoMaterials Registry;**
- **Analyze the consistency and reliability of experimental data for each type of MNPs within the Nanoregistry;**
- **Extract relevant subsets of MNPs tested in the same assay and build predictive QNAR models.**

Industrial Interactions and Technology Transfer

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

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

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

- **RTI (NanoMaterials Registry) – Data collection and curation; QNAR model development**

Publications and Presentations

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

- **Presentation at US-EU NanoEHS Workshop, December 2013, entitled "Nanomaterial Registry"**

us-eu
bridging nanoEHS research efforts

- **D.Fourches, A. Tropsha. Quantitative Nanostructure-Activity Relationships: from Unstructured Data to Predictive Models for Designing Nanomaterials with Controlled Properties. In book: Nanotoxicology: Progress toward Nanomedicine, 2nd Edition, CRC Press, edited by Nancy A. Monteiro-Riviere, C. Lang Tran. ISBN: 9781482203875, available 03/2014.**

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