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Some Fundamentals of Particle Dosimetry for Risk-Directed Studies

June 26, 2023

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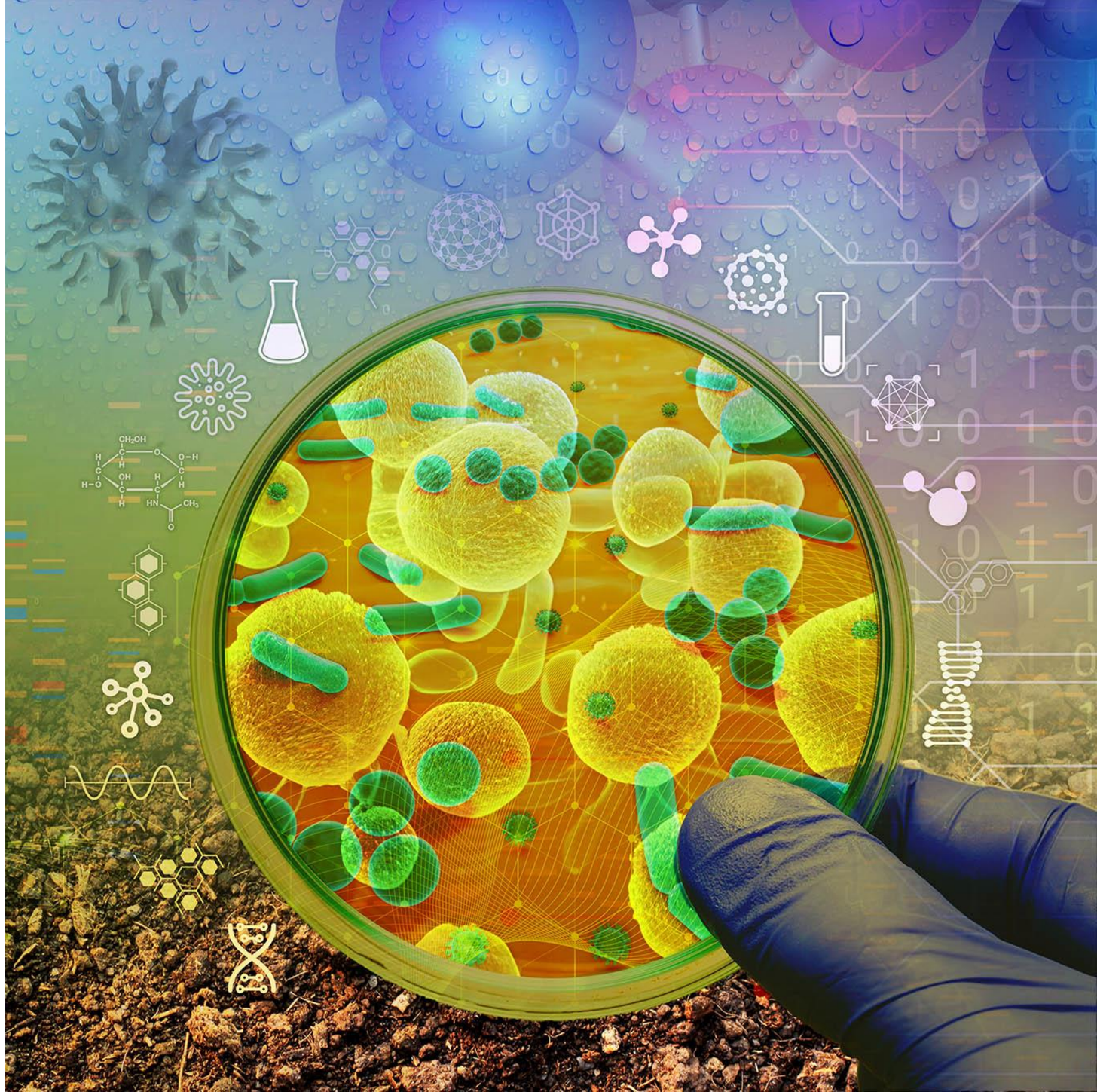

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WHY

Response

Ignore it

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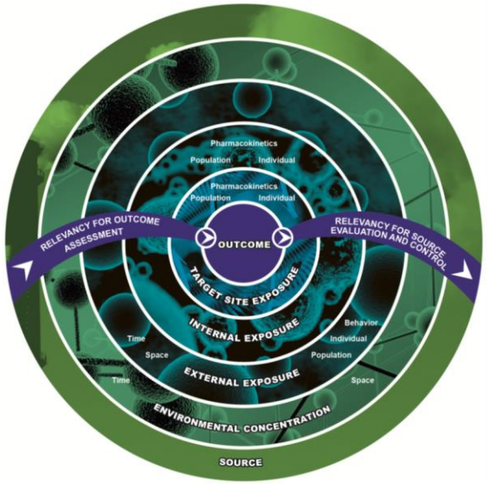
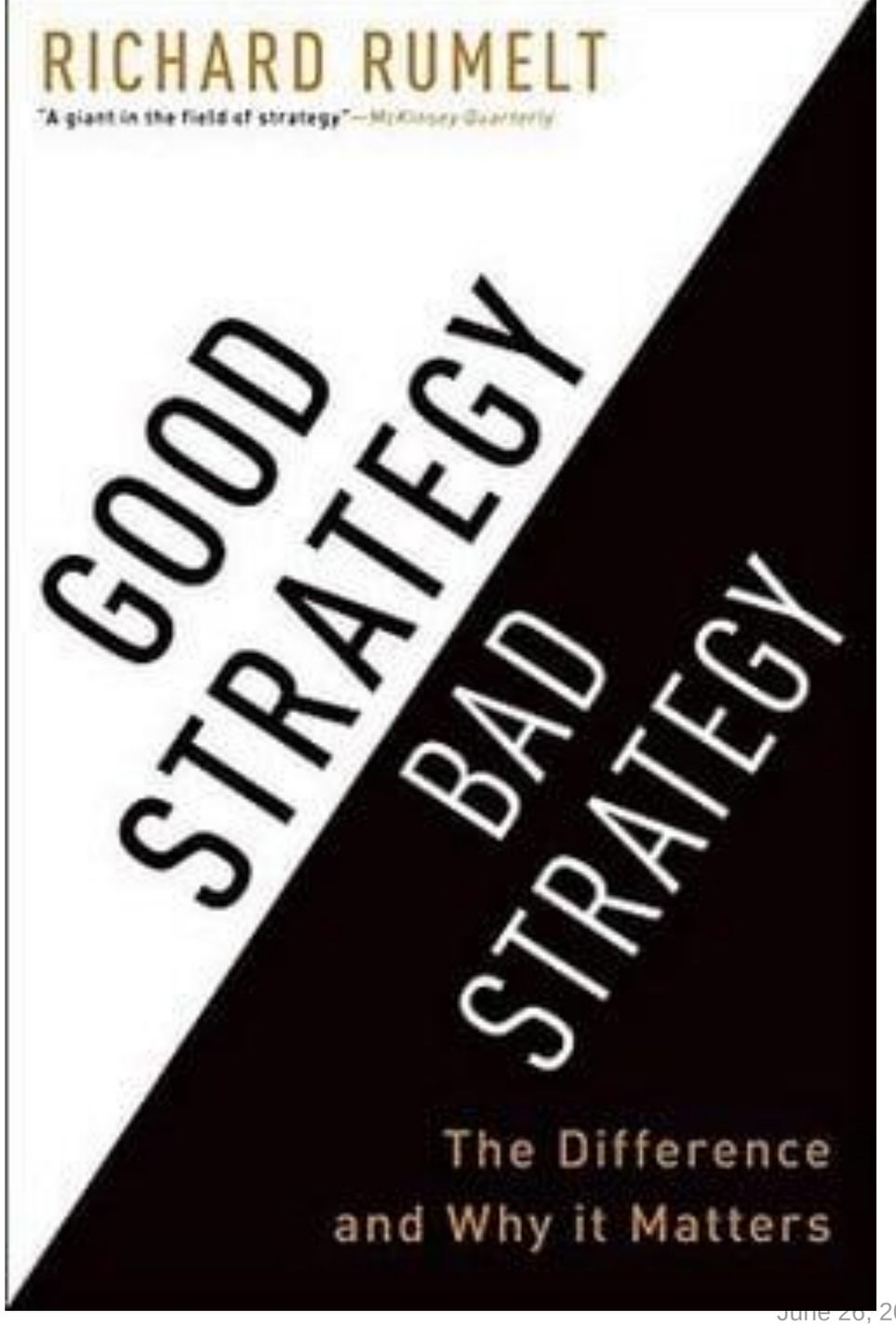
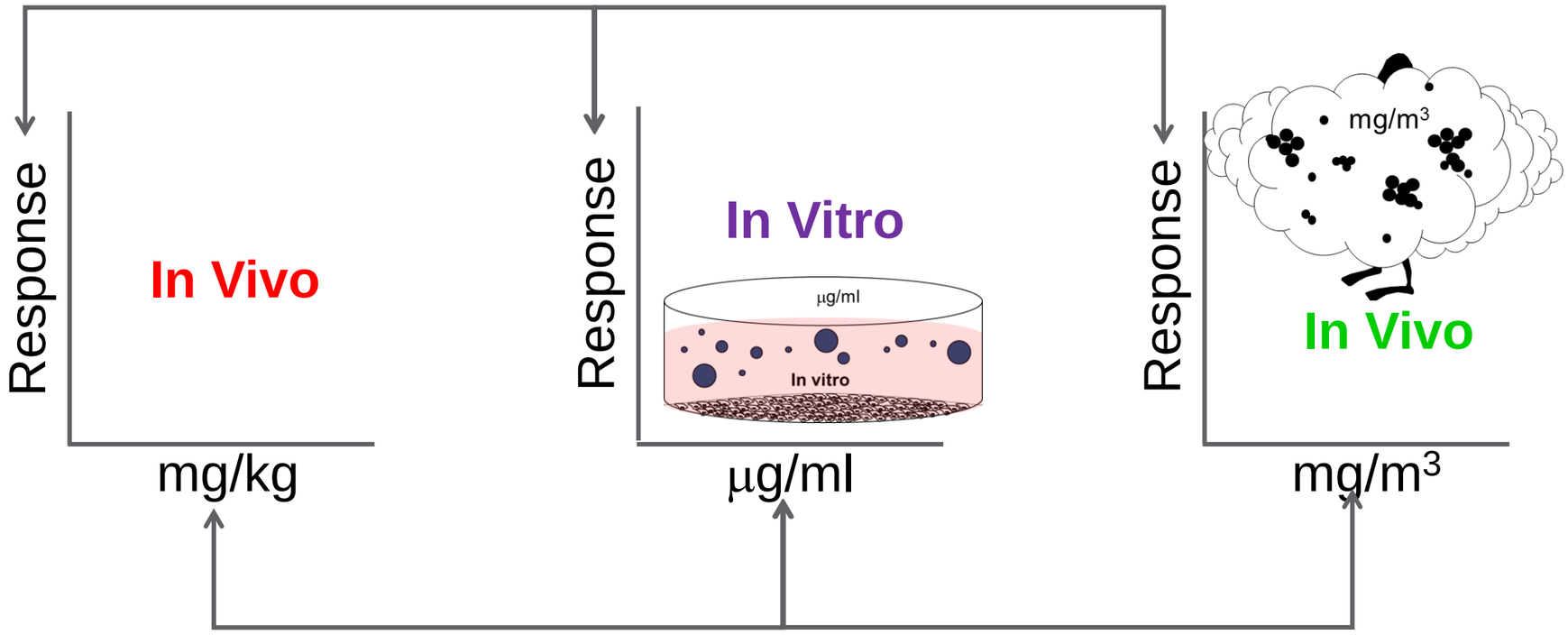
Exposure-driven toxicology and planning for exposure translation are advantages for public health related research





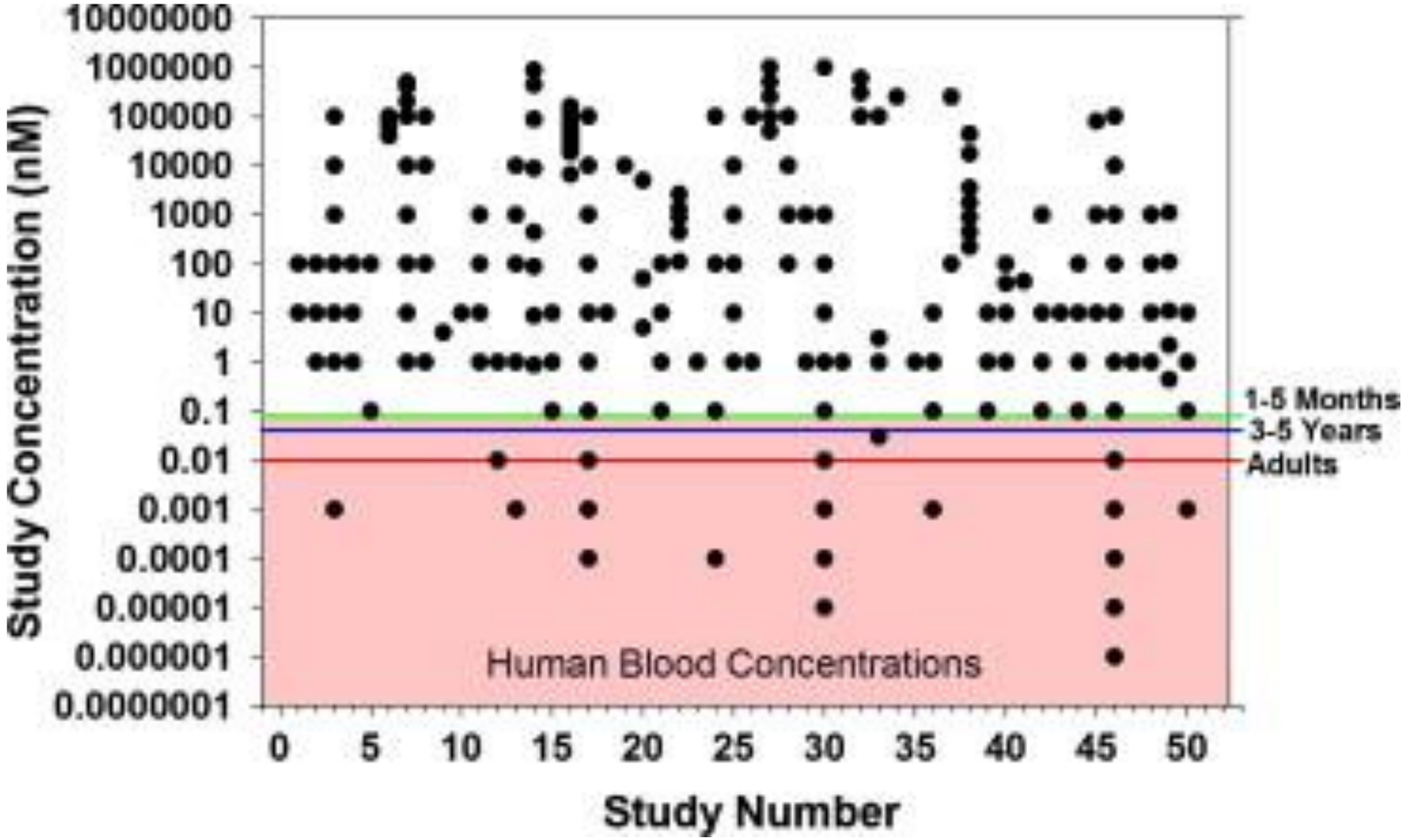
Concordance across Systems for Risk or Hazard Assessment is a Challenge for Toxicology

How Do the Biological Responses Compare?



How Do the Exposure Compare?

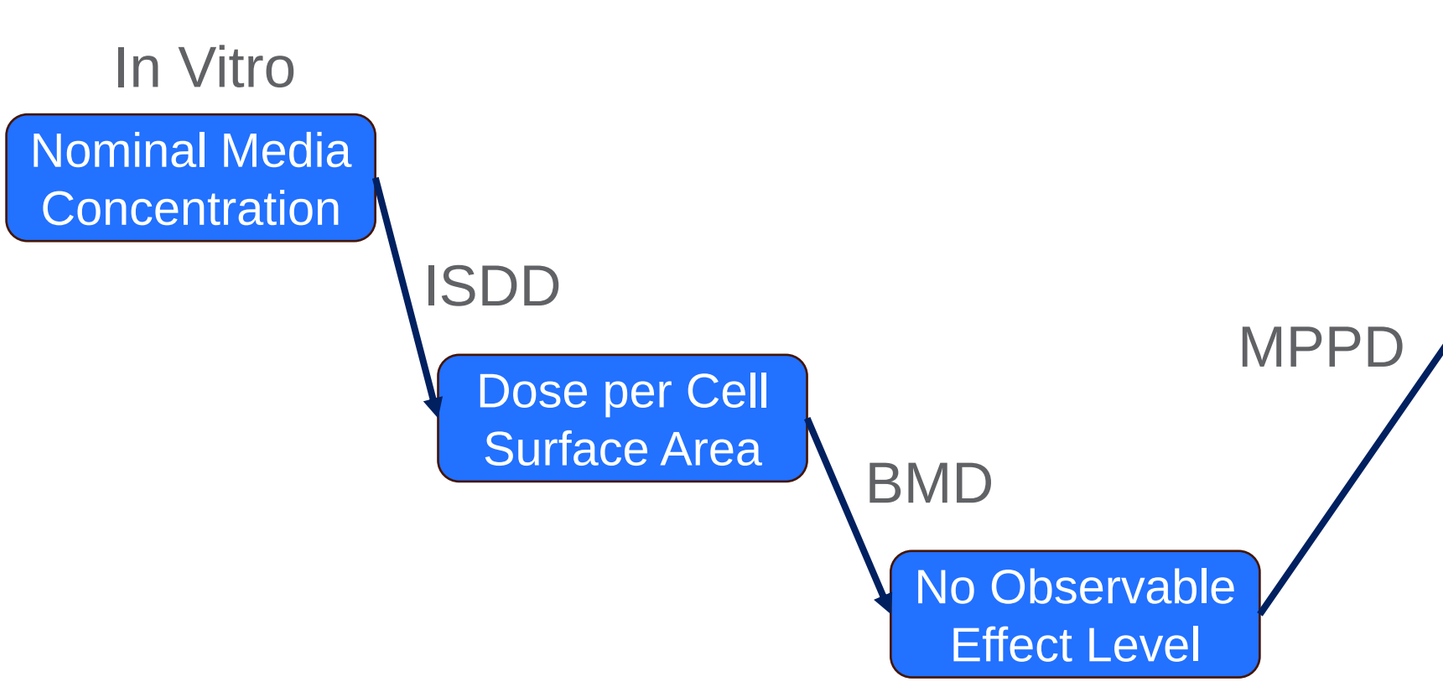
Irrelevant In Vitro Exposures is the Norm



Teeguarden, J.G. and Hanson-Drury, S., 2013. A systematic review of Bisphenol A “low dose” studies in the context of human exposure: A case for establishing standards for reporting “low-dose” effects of chemicals. *Food and chemical toxicology*, *62*, pp.935-948.

**Justin G. Teeguarden, Sesha Hanson-Drury,
Food and Chemical Toxicology, Volume 62, 2013,
Pages 935-948,**

Toxicity Rankings In Vitro do not Relate well to OEL's

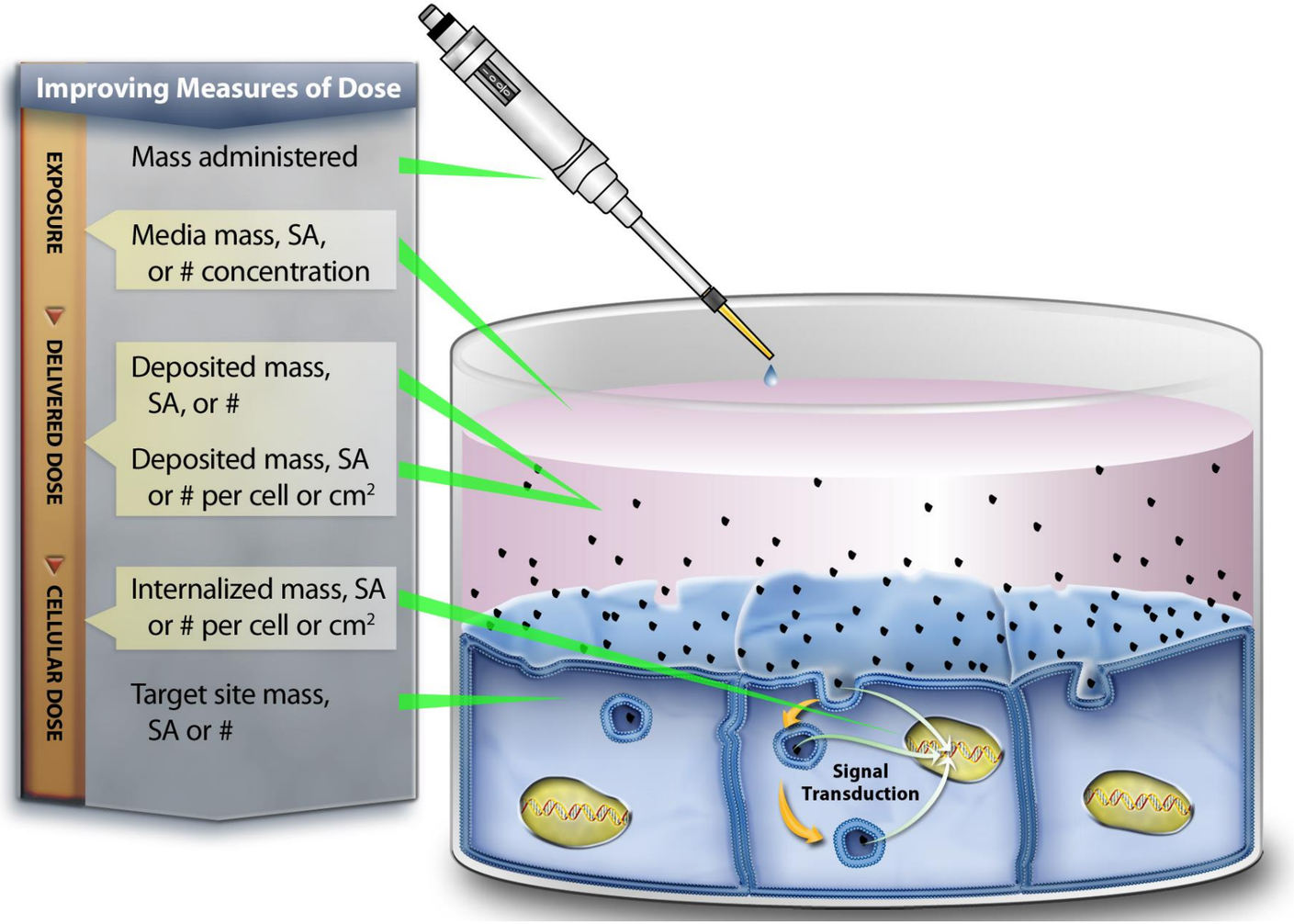


Hazard Ranking

Particle	In Vitro Ranking	Human OEL Ranking
Co_3O_4	10	1
Sb_2O_3	4	2
SiO_2	1	3
CeO_2	12	5
Mn_2O_3	7	6
Ni_2O_3	6	7
CuO	2	4
ZrO_2	3	7
La_2O_3	13	9
ZnO	5	8
Cr_2O_3	9	13
Y_2O_3	11	12
CoO	8	11

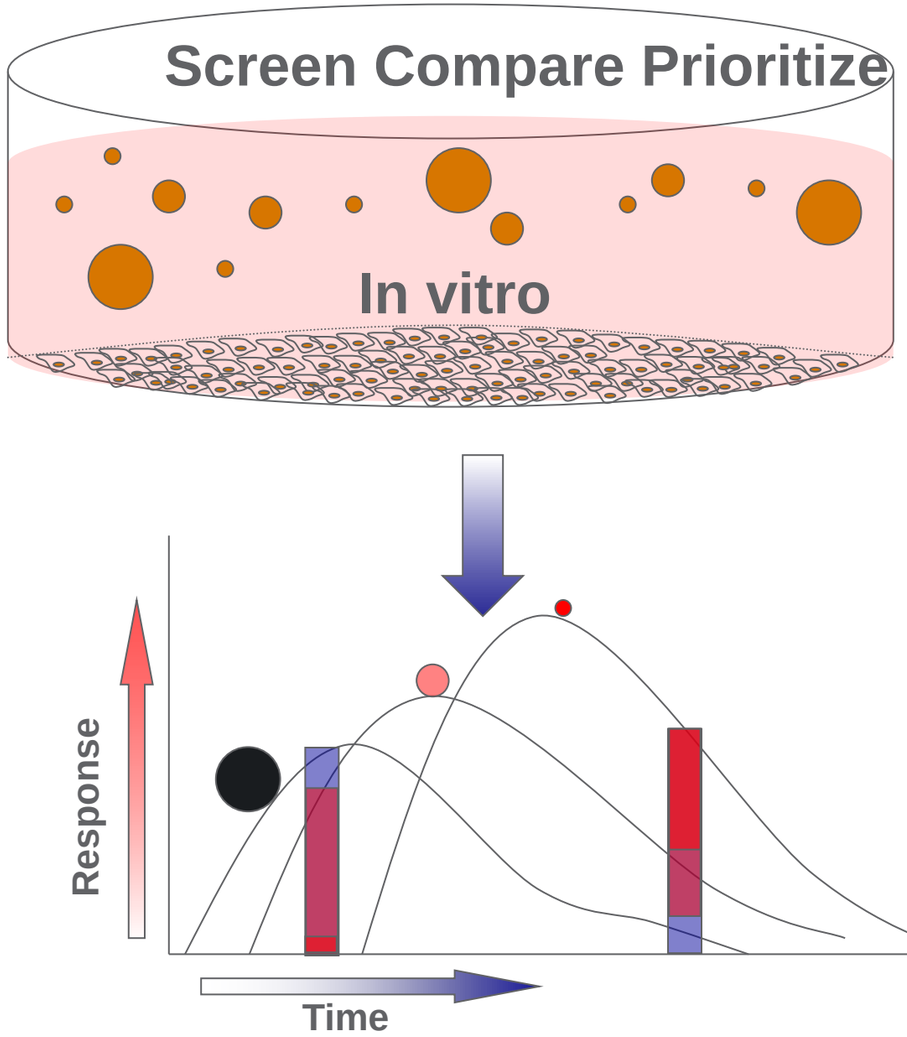
Exposure for Particles is Complicated

- Amount (mass)
- Time
- Surface area
- Size
- Particle Number
- Shape
- Agglomeration state
- Physicochemical prope
- Reactivity
- Dissolution
- Density

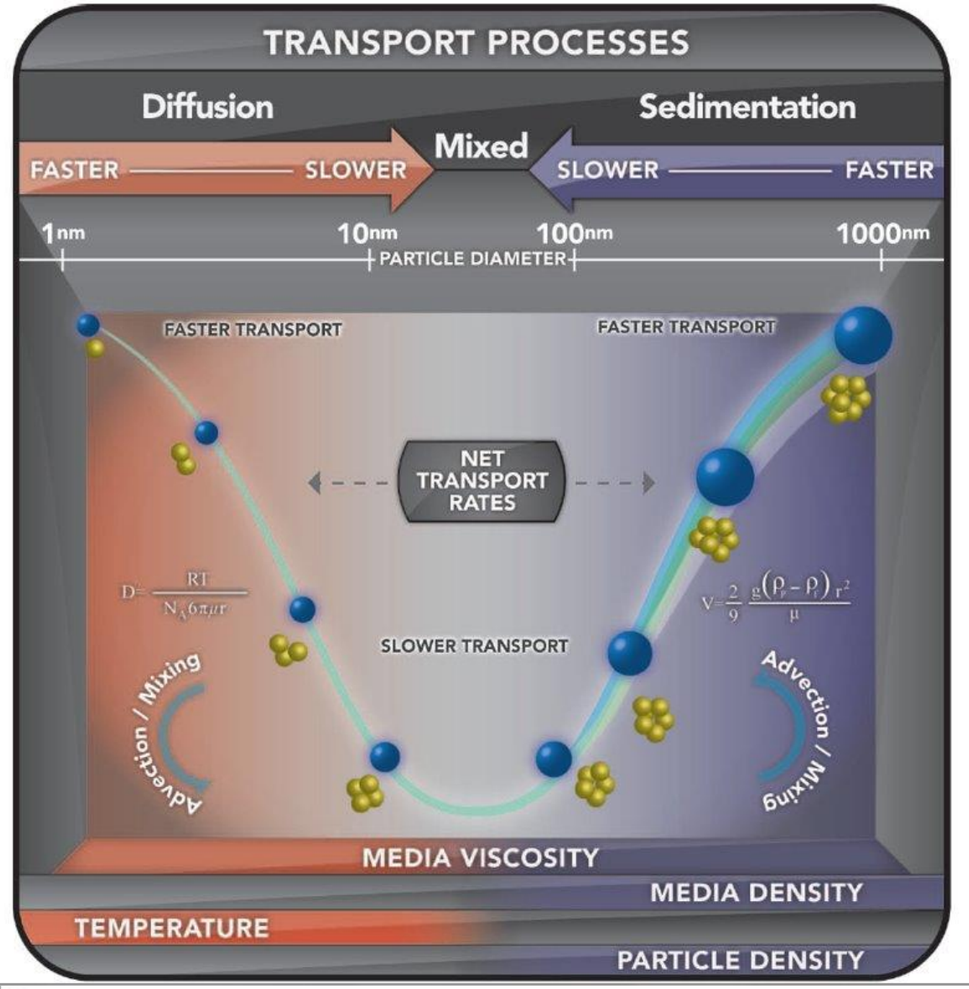


Particokinetics-In Vitro Affects Dosimetry

- **Shape, size, and density affect settling rate.**
- **Settling time impacts timing/magnitude of response**
- **Media “dose” is different than dose to the cell**



The Simple Physics of In Vitro Particokinetics



Particol r *In Vitro*

Justin Pounds

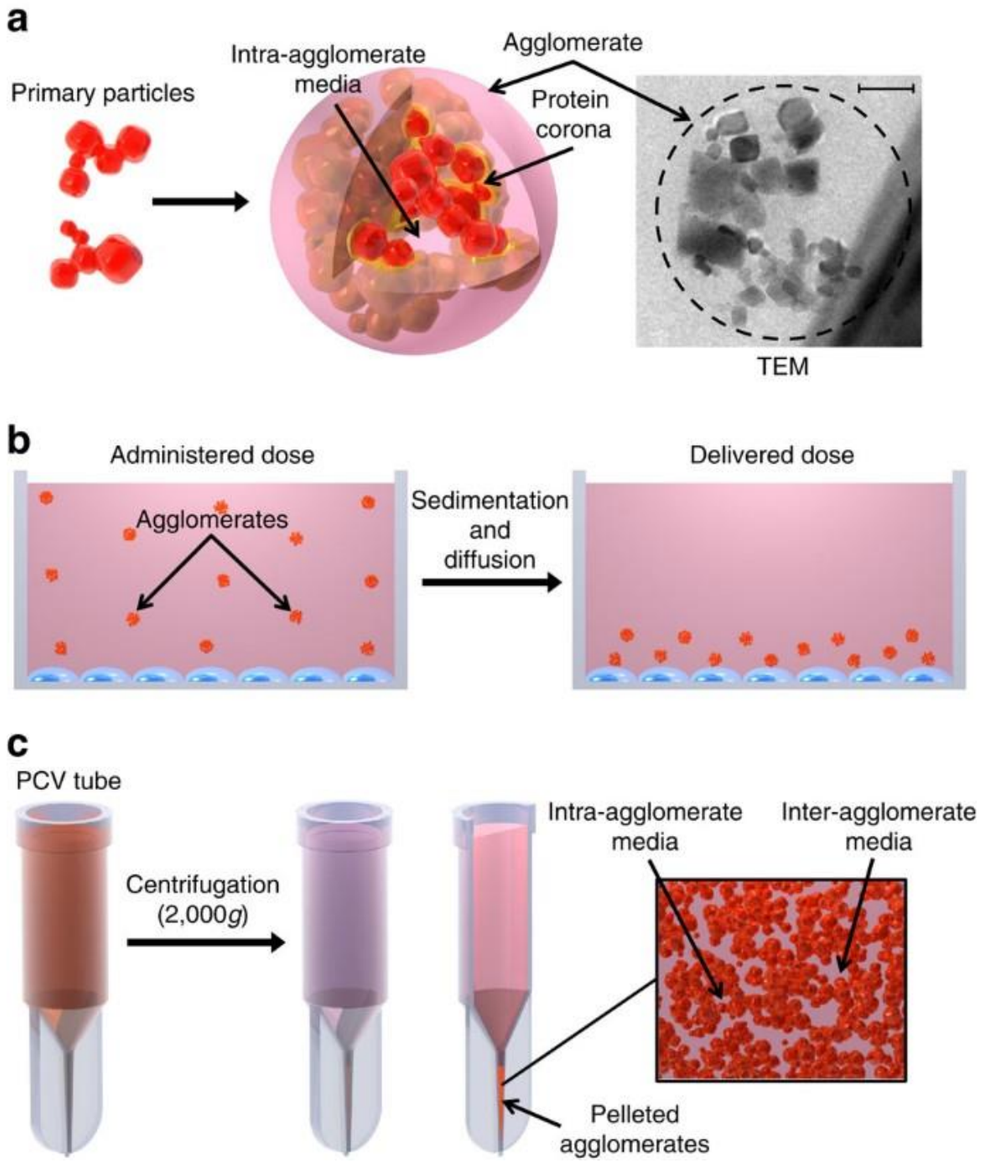
RESEARCH Open Access

ISDD: A c
sediment dosimetry
for *in viti*

Paul M Hinderliter[1],
Justin G Teeguarden[1], G Pounds[1],

Agglomerate Density is Measurable

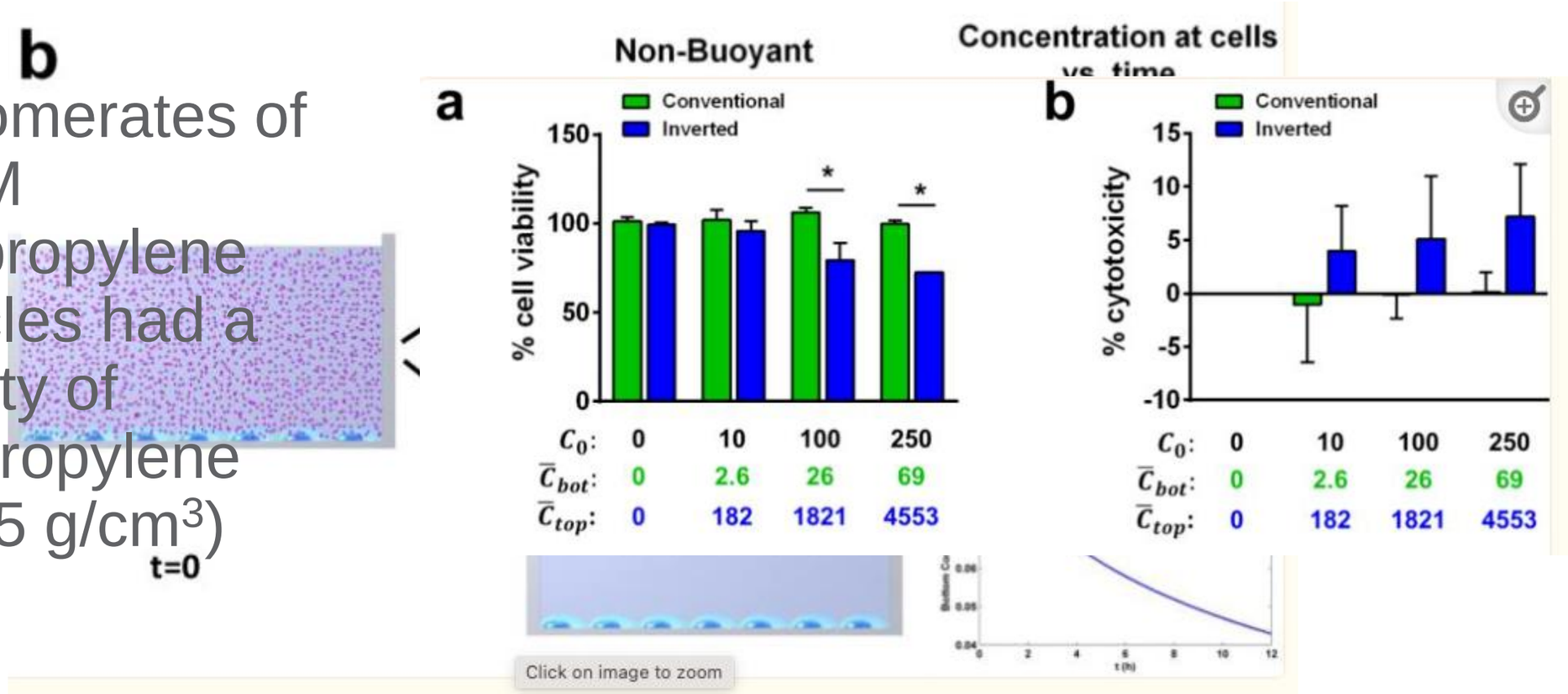
- The VCM-ISDD method improves estimation of agglomerate cellular doses in vitro.



DeLoid, G., Cohen, J., Darrah, T. *et al.* Estimating the effective density of engineered nanomaterials for *in vitro* dosimetry. *Nat Commun* **5**, 3514 (2014). https://doi.org/10.1038/ncomms4514

Buoyancy Impacts Cellular Exposure In Vitro

- Agglomerates of 65 nM Polypropylene particles had a density of polypropylene (0.855 g/cm^3)



Buoyant Nanoparticles: Implications for Nano-biointeractions in Cellular Studies

C.Y. Watson[#], **GM. DeLoid**[#], **A. Pal**, and **P. Demokritou**[*]
Center for Nanotechnology and Nanotoxicology, Department of Environmental Health, Harvard School of Public Health, 655 Huntington Ave Boston, MA 02115

VCM-Distorted Grid Model in Online

Advanced computational modeling for *in vitro* nanomaterial dosimetry

Glen M. DeLoid, Joel M. Cohen, Georgios Pyrgiotakis, Sandra V. Pirela, Anoop Pal, Jiying Liu, Jelena Srebric & Philip Demokritou

Particle and Fibre Toxicology **12**, Article number: 32 (2015) | Cite this article

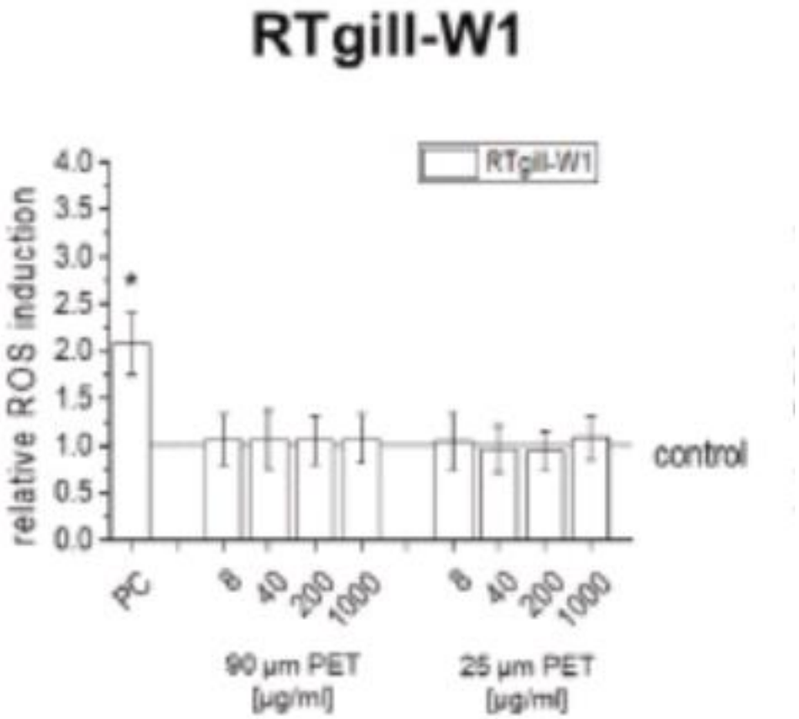
An In Vitro Dosimetry Tool for the Numerical Transport Modeling of Engineered Nanomaterials Powered by the Enalos RiskGONE Cloud Platform

Nikolaos Cheimarios [1], Barbara Pem [2], Andreas Tsoumanis [1], Krunoslav Ilić [2], Ivana Vinković Vrček [2], Georgia Melagraki [3], Dimitrios Bitounis [4], Panagiotis Isigonis [5], Maria Dusinska [6], Iseult Lynch [7], Philip Demokritou [4], Antreas Afantitis [1]

Buoyant Particles are Not Toxic?

Floaters

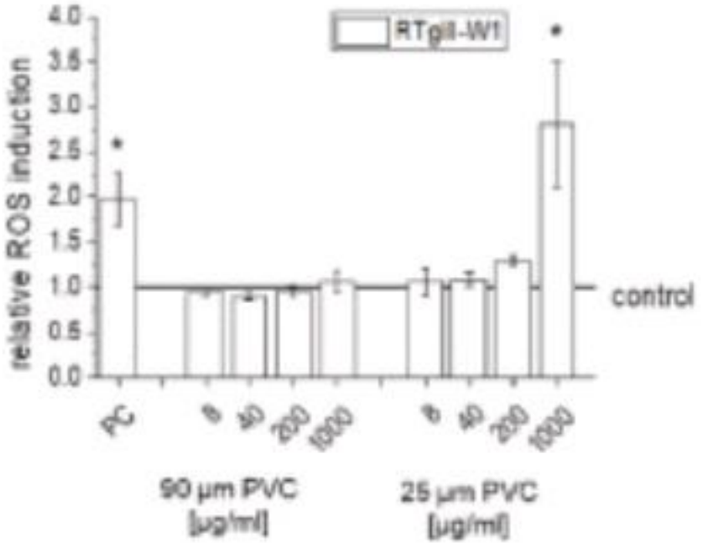
PET



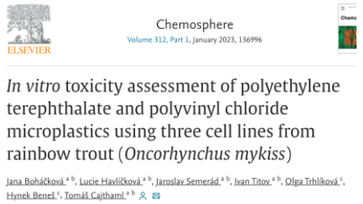
Processed

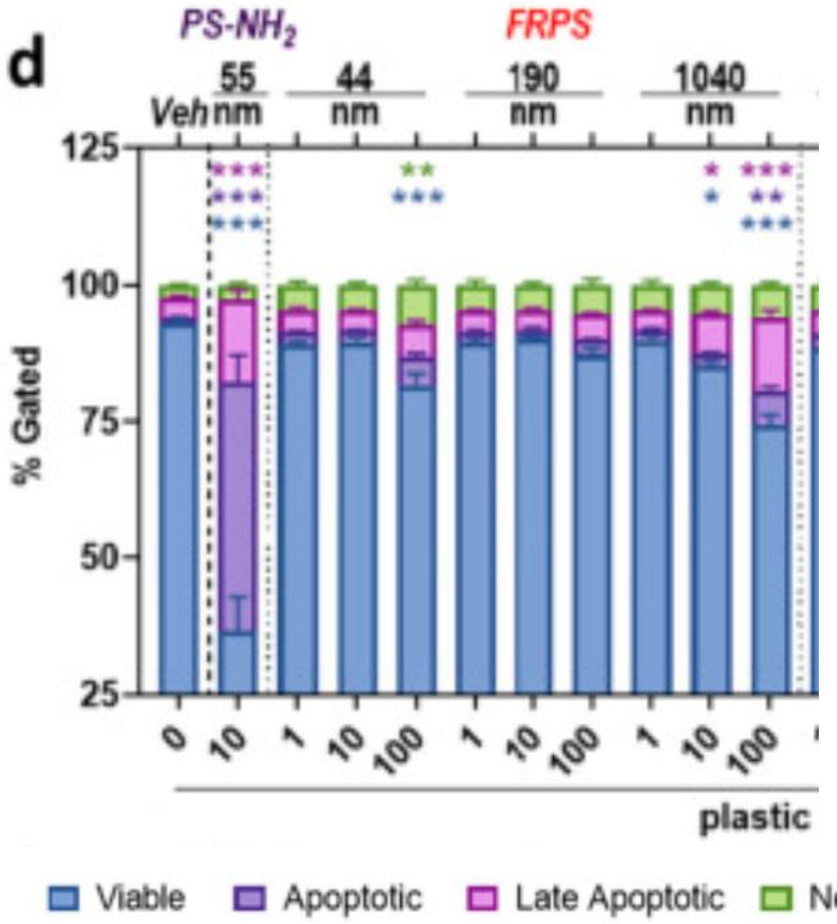
PVC

Sinkers



Boháčková, J., Havlíčková, L., Semerád, J., Titov, I., Trhlíková, O., Beneš, H. and Cajthaml, T., 2023. In vitro toxicity assessment of polyethylene terephthalate and polyvinyl chloride microplastics using three cell lines from rainbow trout (Oncorhynchus mykiss). *Chemosphere*, *312*, p.136996.



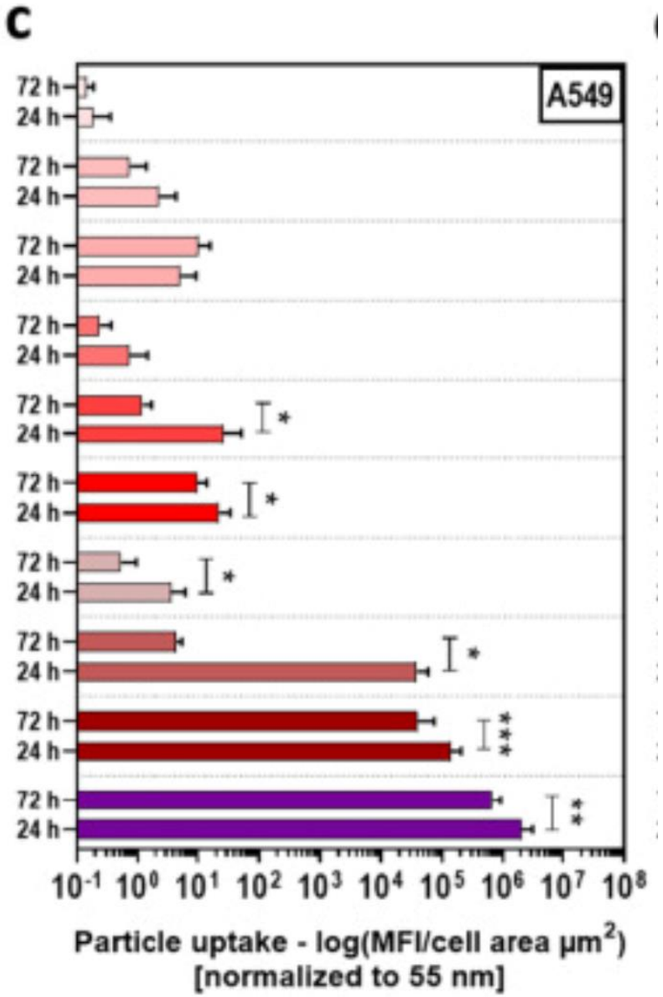


Effect Levels (ug/ml)

10 ug/ml of PS-NH2
100 ug/ml of 44 nM PS
10-100 ug/ml of 1040 nM PS

Effect Levels (uptake)

10 MFI of 44 nM PS
10,000 MFI of 1040 nM PS
100,000 MFI of PS-NH2



da Silva Brito, W.A., Singer, D., Miebach, L., Saadati, F., Wende, K., Schmidt, A. and Bekeschus, S., 2023. Comprehensive in vitro polymer type, concentration, and size correlation analysis to microplastic toxicity and inflammation. *Science of The Total Environment*, *854*, p.158731.

Final Thoughts

- Lead the community to establish a clear quantitative understanding of human exposure
- Set community standards for measuring/modeling and reporting exposures in in vitro studies
- Set community standards for including “relevant” and interpretable exposures in in vitro studies
- Develop methods and tools
- Then study toxicity…

“Exposure-driven toxicology that focuses on real-world exposures…”

Future Directions Workshop: Advancing the Next Scientific Revolution in Toxicology

April 28-29,2022

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Producing data for one axis costs less than half of as much as producing data for two axes, but one-axis data is worthless.