Task ID: 425.025
Task Title: Development of a Quantitative Structure-Activity Relationship for the Prediction of the Biological Effects of Nanoparticles Associated with Semiconductor Industries
Deliverable Name: Report describing critical physicochemical parameters related to the toxicity of engineered nanomaterials. 2) This information is generated largely from an extensive literature survey and provides industry with a framework for determining the properties that govern toxicity.

Summary/Abstract:
To develop a robust quantitative structure-activity relationship (QSAR) model capable of predicting the toxicity of semiconductor nanomaterials, this report summarizes information regarding various physicochemical properties of nanoparticles (NPs), particularly recent experimental results that correlate engineered nanomaterial toxicity to the adhesion force between NPs and cells. The usefulness of adhesion force as a descriptor of NP properties shows that both the composition of NPs and particle size exert significant effects on NP-cell interactions. A correlation between adhesion force and adsorption rate was experimentally derived and validated for the first time, and this model provides insight into the potential impact of different NPs.

Technical Results and Data:
Based on our literature survey, we summarized the physiochemical properties of nanomaterials that are widely identified as potential correlating factors for the toxicological effects observed in *in vivo/in vitro* experiments. Particle size appears to cause the variations in other parameters such as surface area *(1, 2)*, surface charge/charge density *(3-5)*, surface roughness *(6, 7)*, and number concentration *(8, 9)*; these are frequently reported as factors in the stability, mobility, and possible toxicity of NPs to biosystems *(10)*.
As is often observed, in our experiments NP agglomeration and sedimentation in the liquid medium occurred instantly, especially for ultra-small NPs *(9, 11)*. Thus, conventional toxicological experiments typically report the interactions of large NP aggregates rather than individual NPs with biota. For example, our research group measured octanol-water partitioning coefficients (K_{ow}) for five NPs (hematite NPs, silver, fullerene, fullerenol). The results, shown in Figure 1, suggest that unlike the accumulation of organic pollutants in the environment, which largely relies on a single descriptor (K_{ow}), NPs display complex partitioning scenarios (into the octanol phase, water phase, and interface), and pH/ionic strength/presence of natural organic matter all can alter the partitioning state. Thus far it is still hard to predict and explain NP partitioning in the environment based on the outcome of partitioning coefficient experiments due to uncontrollable mechanisms (e.g., aggregation/dissociation leads to size differences under a wide range of pH or ionic strengths). To find new integrative surrogate descriptors for NPs that can reasonably account for the comprehensive properties of NPs during their interactions with aquatic biosystems *(12-15)*, we used atomic force microscopy (AFM) to measure and compare the adhesion forces between different sizes and types of NPs (see Table 1) and two kinds of cell surfaces (*E. coli* and Caco-2). As shown in Figure 2, NP composition varies the adhesion force when the AFM operational parameters [pH 7.2, ionic strength 200 mM, silicon nitride (Si_3N_4) V-shaped cantilevers (Model NPO20, spring constant 0.06 ±0.02 nN/nm, Veeco Instruments Inc. USA), and the initial deflection -1.2 ± 0.1 V] are held constant. Adhesion forces between NPs and *E. coli* or Caco-2 cells were found to decrease as particle size increased, as shown in Figure 3, and our model of the effective contact area well matched the trend of decreasing adhesion force with increasing particle size. This model indicates that small NPs adhere to cell surfaces more strongly than do large NPs. We also demonstrated (see Figure 4) that topographical effects on interfacial energy and depletion attraction may contribute to this size effect. Following the study of the size effect on adhesion force, we established an important connection between adhesion force and the adsorption rate of NPs onto a cell surface; the theoretical relationship can be derived mathematically from the conceptual model in Figure 5-A. Figure 5-B shows the fit between the empirical equation and experimental data, which validated our hypothesis about this connection.

Adhesion force measurement provides a new tool for uncovering the mechanisms behind the behaviors and cytotoxicity of NPs in aqueous environments and the complex interactions with biota, such as the observed partitioning phenomenon. One remarkable advantage of employing AFM to characterize NPs via adhesion force is that fixation of NPs during interactions in an aqueous environment avoids the NP agglomeration and sedimentation that usually hampers toxicological tests.

References:

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Supplementary Materials:

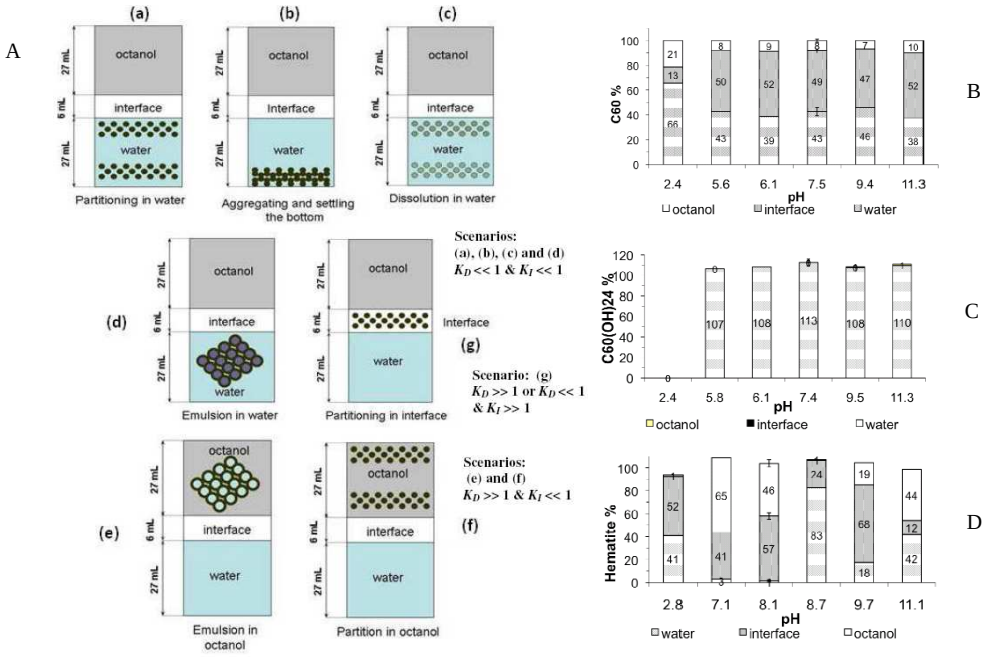

Figure 1 A: Boundary partitioning scenarios (a~g) of nanoparticles in the octanol and aqueous phases and the interface. B: Partitioning of n-C_{60}, C: n-$C_{60}(OH)_{24}$ D: hematite nanoparticles in the interface, octanol, and aqueous phases at different pH values in the presence of 1 mM $NaHCO_3$ buffer.

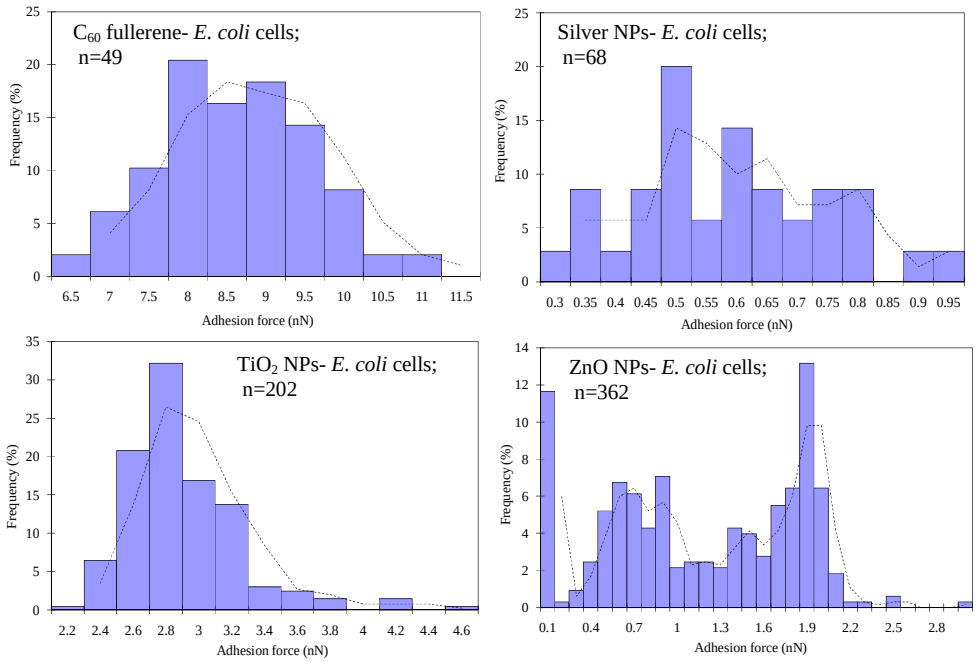

Figure 2 Adhesion force distribution histograms for NPs in 200 mM phosphate buffer solution (PBS, pH≈7.2).

Table 1 Brief information on NPs used in our research (used as received from vendor)

NPs	Size	Density	Surface functional groups	Vendor
Fullerene	0.72 nm	1.72 g/cm^3	no	Sigma Aldrich
NanoSilver	10 nm	10.5 g/cm^3		
TiO_2	15-40 nm	3.9 g/cm^3		
ZnO	50-70 nm	5.61 g/ cm^3		
Hematite	26-150 nm	5.7 g/ cm^3		Lab-synthesized

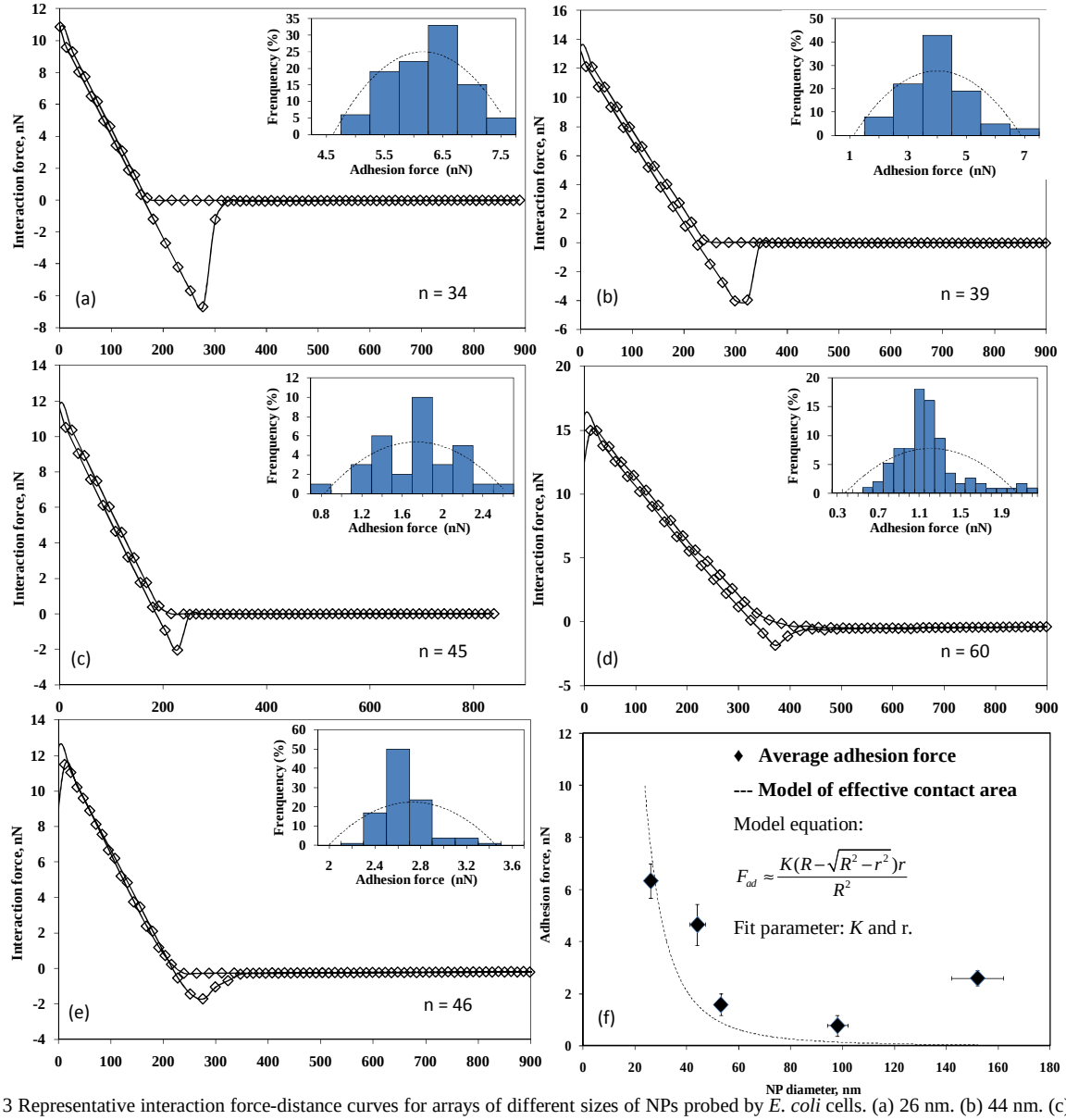

Figure 3 Representative interaction force-distance curves for arrays of different sizes of NPs probed by *E. coli* cells. (a) 26 nm. (b) 44 nm. (c) 53 nm. (d) 98 nm. (e) 152 nm. (f) Average adhesion force for different sizes of NPs (horizontal error bars indicate standard deviation of particle diameter, and vertical error bars indicate standard deviation of adhesion force). n is the number of force measurements for each sample.

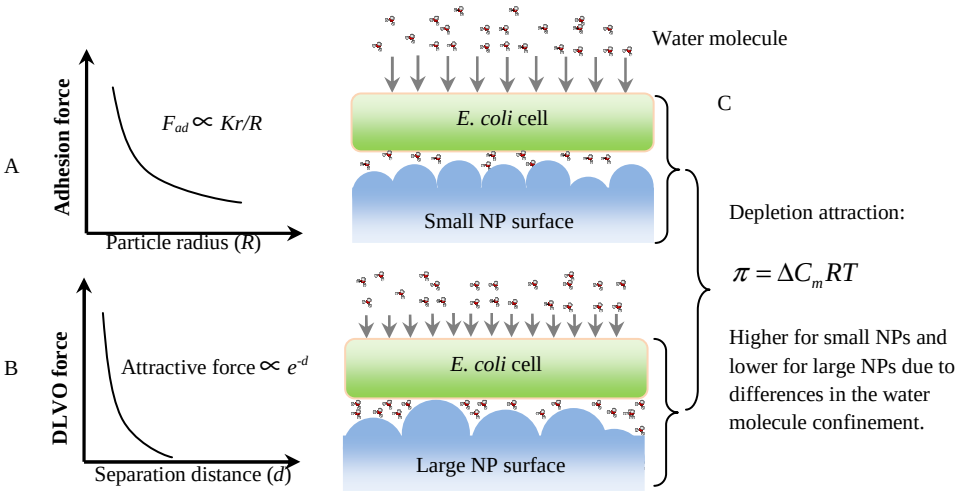

Figure 4 Representation of potential mechanism of size effect on adhesion force. A. Relationship between adhesion force (F_{ad}) and particle radius (R) (K and r are the model parameters;. Exponential decay of the Derjaguin–Landau–Verwey–Overbeek (DLVO) forces with distance. C. Depletion attraction (potentially different for cell surfaces interacting with different sizes of NPs.

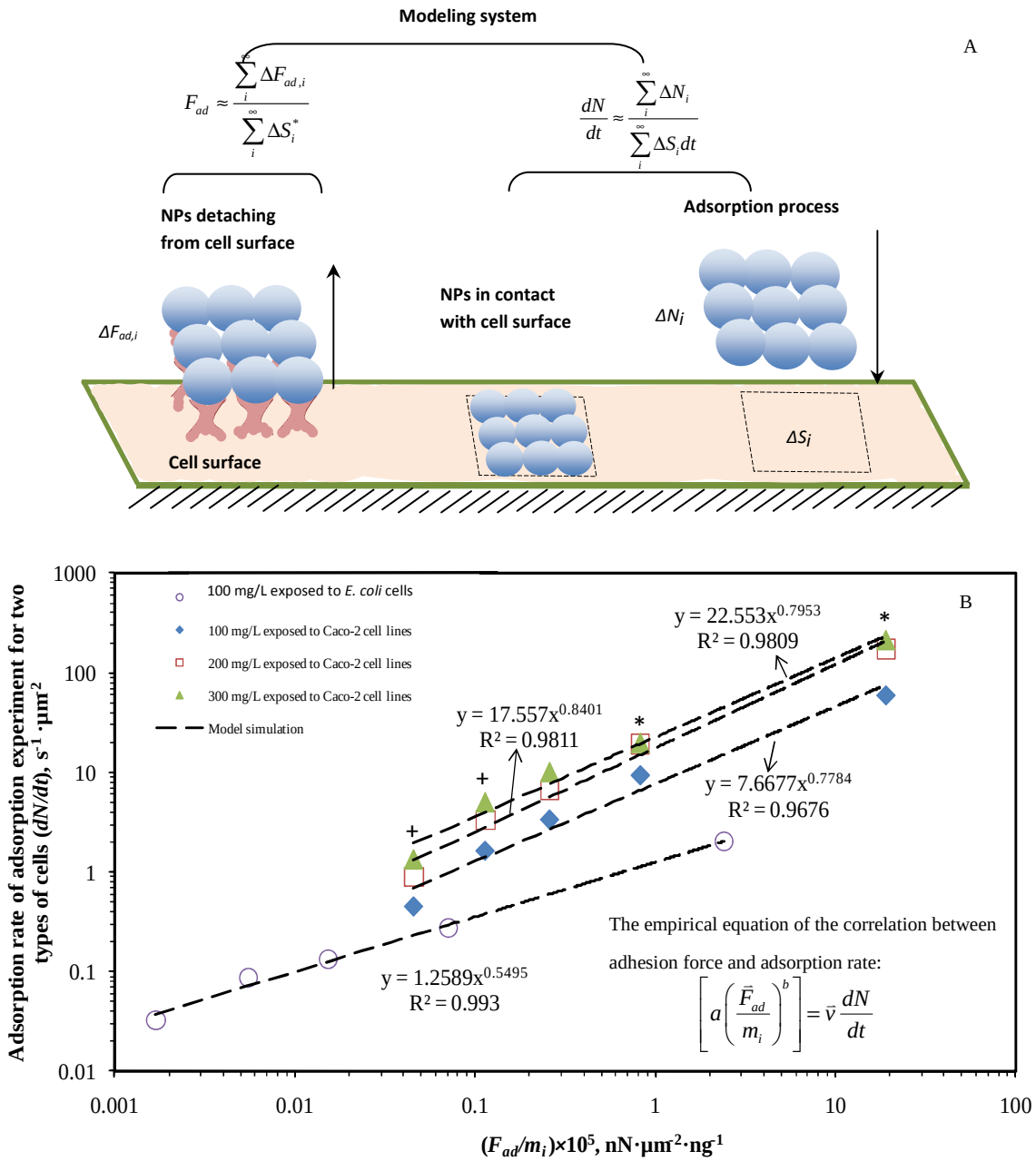

Figure 5. A: Conceptual model of the relation between adhesion force and adsorption rate (*dN/dt*). B: Comparison of the model simulation (dotted line) and experimental data. Symbols (* and +) indicate a significant difference ($p<0.05$) between the groups of three points marked by (+) and those groups marked by (*).