

Supporting Information for:

Iron oxide nanoparticle-induced neoplastic-like cell transformation *in vitro* is reduced with protective amorphous silica coating.

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Table S1: Particle dosimetry with repeated sonications.^a

# Sonic.	nFe ₂ O ₃			SiO ₂ -nFe ₂ O ₃			GMA-MS			SiO ₂			TiO ₂		
	d _H (h, Z avg.)	Avg. Fraction Dep. (2hr)	Avg. Fraction Dep. (24hr)	d _H (h, Z avg.)	Avg. Fraction Dep. (2hr)	Avg. Fraction Dep. (24hr)	d _H (h, Z avg.)	Avg. Fraction Dep. (2hr)	Avg. Fraction Dep. (24hr)	d _H (h, Z avg.)	Avg. Fraction Dep. (2hr)	Avg. Fraction Dep. (24hr)	d _H (h, Z avg.)	Avg. Fraction Dep. (2hr)	Avg. Fraction Dep. (24hr)
1	2570	0.799	0.979	1895	0.600	0.921	1114	0.712	0.938	1774	0.333	0.704	2085	0.773	0.973
2	1569	0.774	0.972	1570	0.639	0.939	1239	0.781	0.969	1078	0.174	0.570	2007	0.773	0.973
3	1758	0.785	0.975	1539	0.607	0.927	1119	0.773	0.965	760	0.101	0.451	1309	0.680	0.949
4	1550	0.762	0.969	1311	0.560	0.907	1123	0.763	0.961	590	0.016	0.114	1507	0.712	0.957
5	1541	0.713	0.954	1287	0.571	0.917	1185	0.780	0.969	729	0.031	0.179	1164	0.615	0.927
6	1343	0.701	0.951	1150	0.499	0.884	844	0.714	0.943	555	0.015	0.100	1441	0.782	0.975
7	1428	0.763	0.970	1392	0.601	0.923	1244	0.781	0.970	588	0.017	0.118	1947	0.785	0.976
8	1603	0.766	0.970	1149	0.467	0.865	1047	0.770	0.966	513	0.015	0.096	1440	0.705	0.956

^a Particle size measured using dynamic light scattering (DLS), and incorporated into distorted grid (DG) fate and transport modeling algorithm. Each repeat sonication was conducted 3-4 days following previous one. Avg: Average. Dep: Deposition. Sonic: sonications.

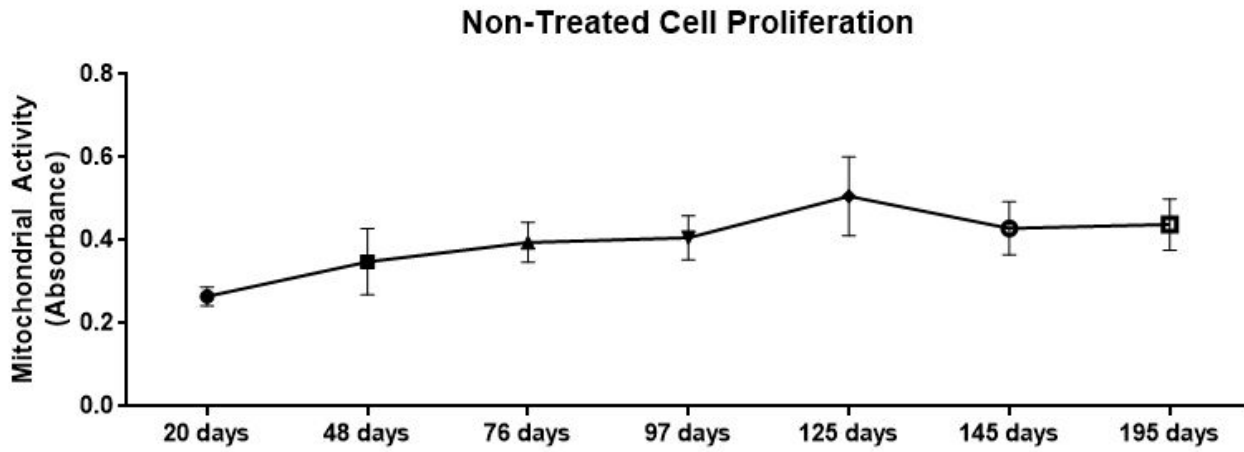


Figure S1. Non-treated cell proliferation throughout sub-chronic exposure, using raw absorbance of WST1 assay as a measurement. There were no significant differences in activity across the exposure period.

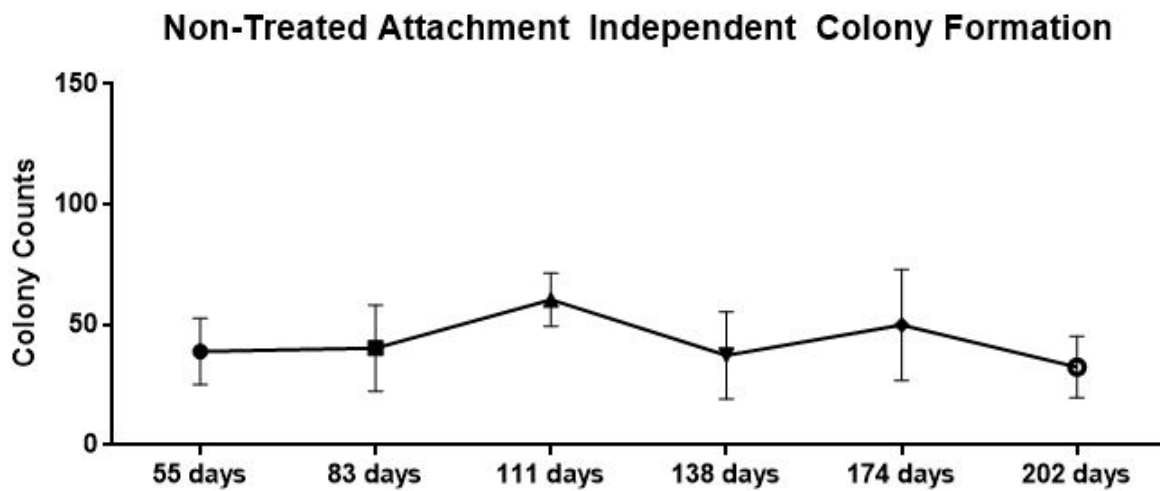


Figure S2. Attachment independent colony formation of non-treated control cells throughout sub-chronic exposure, shown in raw colony counts. There were no significant differences in this parameter throughout the exposure period.

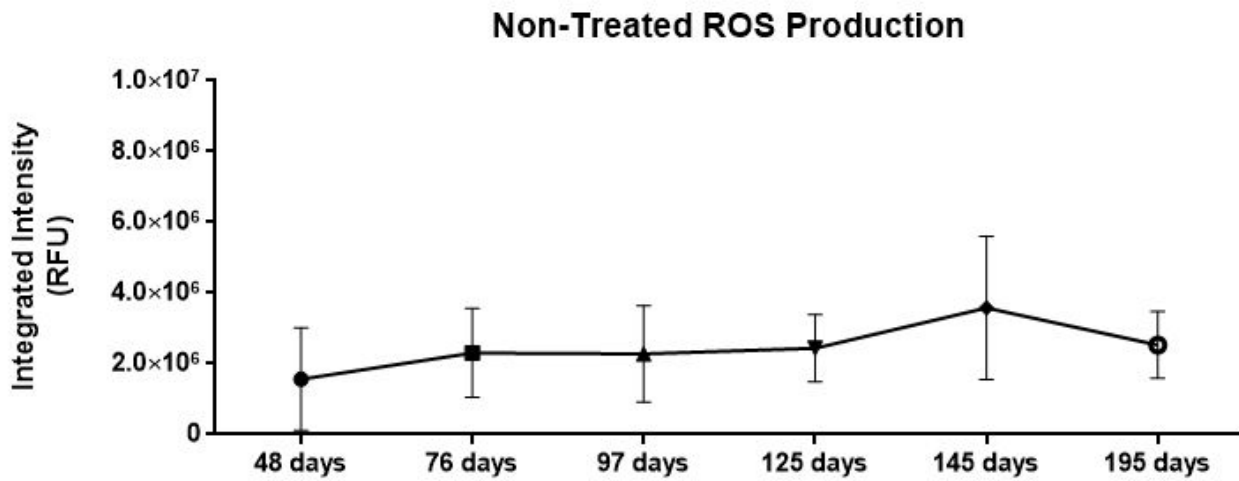


Figure S3. ROS production of non-treated control cells throughout sub-chronic exposure, shown in raw fluorescent units. There were no significant changes in this parameter throughout the exposure period.

REFERENCES FOR COMPLETE MANUSCRIPT

- (1) Starmans, L. W. E.; Burdinski, D.; Haex, N. P. M.; Moonen, R. P. M.; Strijkers, G. J.; Nicolay, K.; Gröll, H. Iron Oxide Nanoparticle-Micelles (ION-Micelles) for Sensitive (Molecular) Magnetic Particle Imaging and Magnetic Resonance Imaging. *PLoS One* 2013, 8 (2), e57335.
- (2) Unterweger, H.; Tietze, R.; Janko, C.; Zaloga, J.; Lyer, S.; Taccardi, N.; Goudouri, M.; Hoppe, A.; Eberbeck, D.; Schubert, D.; et al. Development and Characterization of Magnetic Iron Oxide Nanoparticles with a Cisplatin-Bearing Polymer Coating for Targeted Drug Delivery. *Int. J. Nanomedicine* 2014, 9, 3659.
- (3) Gonçalves, M.; Guerreiro, M. C.; de Oliveira, L. C. A.; de Castro, C. S. A Friendly Environmental Material: Iron Oxide Dispersed over Activated Carbon from Coffee Husk for Organic Pollutants Removal. *J. Environ. Manage.* 2013, 127, 206–211.
- (4) Sotiriou, G. A.; Singh, D.; Zhang, F.; Chalbot, M.-C. G.; Spielman-Sun, E.; Hoering, L.; Kavouras, I. G.; Lowry, G. V.; Wohlleben, W.; Demokritou, P. Thermal Decomposition of Nano-Enabled Thermoplastics: Possible Environmental Health and Safety Implications. *J. Hazard. Mater.* 2016, 305, 87–95.
- (5) Singh, D.; Schiffman, L. A.; Watson-Wright, C.; Sotiriou, G. A.; Oyanedel-Craver, V.; Wohlleben, W.; Demokritou, P. Nanofiller Presence Enhances Polycyclic Aromatic Hydrocarbon (PAH) Profile on Nanoparticles Released during Thermal Decomposition of Nano-Enabled Thermoplastics: Potential Environmental Health Implications. *Environ. Sci. Technol.* 2017.
- (6) DeLoid, G. M.; Wang, Y.; Kapronezai, K.; Lorente, L. R.; Zhang, R.; Pyrgiotakis, G.; Konduru, N. V.; Ericsson, M.; White, J. C.; De La Torre-Roche, R.; et al. An Integrated Methodology for Assessing the Impact of Food Matrix and Gastrointestinal Effects on the Biokinetics and Cellular Toxicity of Ingested Engineered Nanomaterials. *Part. Fibre Toxicol.* 2017, 14 (1).
- (7) Pirela, S. V.; Sotiriou, G. A.; Bello, D.; Shafer, M.; Bunker, K. L.; Castranova, V.; Thomas, T.; Demokritou, P. Consumer Exposures to Laser Printer-Emitted Engineered Nanoparticles: A Case Study of Life-Cycle Implications from Nano-Enabled Products. *Nanotoxicology* 2015, 9 (6), 760–768.

- (8) Servin, A. D.; White, J. C. Nanotechnology in Agriculture: Next Steps for Understanding Engineered Nanoparticle Exposure and Risk. *NanoImpact* 2016, 1, 9–12.
- (9) De La Torre Roche, R.; Pagano, L.; Majumdar, S.; Eitzer, B. D.; Zuverza-Mena, N.; Ma, C.; Servin, A. D.; Marmioli, N.; Dhankher, O. P.; White, J. C. Co-Exposure of Imidacloprid and Nanoparticle Ag or CeO₂ to Cucurbita Pepo (Zucchini): Contaminant Bioaccumulation and Translocation. *NanoImpact* 2018, 11, 136–145.
- (10) Cai, F.; Wu, X.; Zhang, H.; Shen, X.; Zhang, M.; Chen, W.; Gao, Q.; White, J. C.; Tao, S.; Wang, X. Impact of TiO₂nanoparticles on Lead Uptake and Bioaccumulation in Rice (*Oryza Sativa* L.). *NanoImpact* 2017, 5, 101–108.
- (11) Wild, P.; Bourgard, E.; Paris, C. Lung Cancer and Exposure to Metals: The Epidemiological Evidence. *Methods Mol. Biol.* 2009, 472, 139–167.
- (12) Baldauf, R. W.; Devlin, R. B.; Gehr, P.; Giannelli, R.; Hassett-Sipple, B.; Jung, H.; Martini, G.; McDonald, J.; Sacks, J. D.; Walker, K. Ultrafine Particle Metrics and Research Considerations: Review of the 2015 UFP Workshop. *Int. J. Environ. Res. Public Health* 2016, 13 (11).
- (13) Kobayashi, N.; Naya, M.; Endoh, S.; Maru, J.; Yamamoto, K.; Nakanishi, J. Comparative Pulmonary Toxicity Study of Nano-TiO₂ Particles of Different Sizes and Agglomerations in Rats: Different Short- and Long-Term Post-Instillation Results. *Toxicology* 2009, 264 (1–2), 110–118.
- (14) Duffin, R.; Tran, L.; Brown, D.; Stone, V.; Donaldson, K. Proinflammogenic Effects of Low-Toxicity and Metal Nanoparticles In Vivo and In Vitro: Highlighting the Role of Particle Surface Area and Surface Reactivity. *Inhal. Toxicol.* 2008, 19 (10), 849–856.
- (15) Kennaway, E. L.; Kennaway, N. M. A Further Study of the Incidence of Cancer of the Lung and Larynx. *Br. J. Cancer* 1947, 1 (3), 260–298.
- (16) Moulin, J. J.; Clavel, T.; Roy, D.; Dananche, B.; Marquis, N.; Fevotte, J.; Fontana, J. M. Risk of Lung Cancer in Workers Producing Stainless Steel and Metallic Alloys. *Int Arch Occup Environ. Heal.* 2000, 73 (3), 171–180.

- (17) Faulds, J. S.; Stewart, M. J. Carcinoma of the Lung in Hæmatite Miners. *J. Pathol. Bacteriol.* 1956, 72 (2), 353–366.
- (18) Bourgkard, E.; Wild, P.; Courcot, B.; Diss, M.; Ettliger, J.; Goutet, P.; Hemon, D.; Marquis, N.; Mur, J. M.; Rigal, C.; et al. Lung Cancer Mortality and Iron Oxide Exposure in a French Steel-Producing Factory. *Occup Env. Med* 2009, 66 (3), 175–181.
- (19) Teculescu, D.; Albu, A. Pulmonary Function in Workers Inhaling Iron Oxide Dust. *Int Arch Arbeitsmed* 1973, 31 (2), 163–170.
- (20) Turner, H. M.; Grace, H. G. An Investigation into Cancer Mortality among Males in Certain Sheffield Trades. *J. Hyg. (Lond).* 1938, 38 (1), 90–103.
- (21) Boyd, J. T.; Doll, R.; Faulds, J. S.; Leiper, J. Cancer of the Lung in Iron Ore (Haematite) Miners. *Br J Ind Med* 1970, 27 (2), 97–105.
- (22) Siew, S. S.; Kauppinen, T.; Kyyronen, P.; Heikkila, P.; Pukkala, E. Exposure to Iron and Welding Fumes and the Risk of Lung Cancer. *Scand J Work Env. Heal.* 2008, 34 (6), 444–450.
- (23) Chen, S. Y.; Hayes, R. B.; Liang, S. R.; Li, Q. G.; Stewart, P. A.; Blair, A. Mortality Experience of Haematite Mine Workers in China. *Br J Ind Med* 1990, 47 (3), 175–181.
- (24) Pelclova, D.; Zdimal, V.; Kacer, P.; Fenclova, Z.; Vlckova, S.; Syslova, K.; Navratil, T.; Schwarz, J.; Zikova, N.; Barosova, H.; et al. Oxidative Stress Markers Are Elevated in Exhaled Breath Condensate of Workers Exposed to Nanoparticles during Iron Oxide Pigment Production. *J Breath Res* 2016, 10 (1), 16004.
- (25) Xing, M.; Zhang, Y.; Zou, H.; Quan, C.; Chang, B.; Tang, S.; Zhang, M. Exposure Characteristics of Ferric Oxide Nanoparticles Released during Activities for Manufacturing Ferric Oxide Nanomaterials. *Inhal Toxicol* 2015, 27 (3), 138–148.
- (26) Coricovac, D.-E.; Moacă, E.-A.; Pinzaru, I.; Cîtu, C.; Soica, C.; Mihali, C.-V.; Păcurariu, C.; Tutelyan, V. A.; Tsatsakis, A.; Dehelean, C.-A. Biocompatible Colloidal Suspensions Based on Magnetic Iron Oxide Nanoparticles: Synthesis, Characterization and Toxicological Profile. *Front. Pharmacol.* 2017, 8, 154.

- (27) Freyria, F. S.; Bonelli, B.; Tomatis, M.; Ghiazza, M.; Gazzano, E.; Ghigo, D.; Garrone, E.; Fubini, B. Hematite Nanoparticles Larger than 90 Nm Show No Sign of Toxicity in Terms of Lactate Dehydrogenase Release, Nitric Oxide Generation, Apoptosis, and Comet Assay in Murine Alveolar Macrophages and Human Lung Epithelial Cells. *Chem Res Toxicol* 2012, 25 (4), 850–861.
- (28) Karlsson, H. L.; Gustafsson, J.; Cronholm, P.; Moller, L. Size-Dependent Toxicity of Metal Oxide Particles--a Comparison between Nano- and Micrometer Size. *Toxicol Lett* 2009, 188 (2), 112–118.
- (29) Totsuka, Y.; Ishino, K.; Kato, T.; Goto, S.; Tada, Y.; Nakae, D.; Watanabe, M.; Wakabayashi, K. Magnetite Nanoparticles Induce Genotoxicity in the Lungs of Mice via Inflammatory Response. *Nanomaterials* 2014, 4 (1), 175–188.
- (30) Ishino, K.; Kato, T.; Kato, M.; Shibata, T.; Watanabe, M.; Wakabayashi, K.; Nakagama, H.; Totsuka, Y. Comprehensive DNA Adduct Analysis Reveals Pulmonary Inflammatory Response Contributes to Genotoxic Action of Magnetite Nanoparticles. *Int J Mol Sci* 2015, 16 (2), 3474–3492.
- (31) Bhattacharya, K.; Davoren, M.; Boertz, J.; Schins, R. P.; Hoffmann, E.; Dopp, E. Titanium Dioxide Nanoparticles Induce Oxidative Stress and DNA-Adduct Formation but Not DNA-Breakage in Human Lung Cells. *Part Fibre Toxicol* 2009, 6, 17.
- (32) Watson, C.; Ge, J.; Cohen, J.; Pyrgiotakis, G.; Engelward, B. P.; Demokritou, P. High-Throughput Screening Platform for Engineered Nanoparticle-Mediated Genotoxicity Using CometChip Technology. *ACS Nano* 2014, 8 (3), 2118–2133.
- (33) Sighinolfi, G. L.; Artoni, E.; Gatti, A. M.; Corsi, L. Carcinogenic Potential of Metal Nanoparticles in BALB/3T3 Cell Transformation Assay. *Env. Toxicol* 2016, 31 (5), 509–519.
- (34) Stueckle, T. A.; Davidson, D. C.; Derk, R.; Kornberg, T. G.; Schwegler-Berry, D.; Demokritou, P.; Luanpitpong, S.; Rojanasakul, Y.; Wang, L. Evaluation on Carcinogenesis Potential of Fe₂O₃ and CeO₂ Nanoparticles by a Rapid in Vitro Screening Model. *NanoImpact* 2016, 11 (1).

- (35) Zeidler-Erdely, P. C.; Salmen, R.; Erdely, A.; Keane, M.; Kodali, V.; Antonini, F.; Falcone, L. Pulmonary Toxicity of Gas Metal Arc-Stainless Steel Welding Fume and Component Metals. *Toxicol.* 2017, 150 (1), 2125.
- (36) Falcone, L. M.; Erdely, A.; Kodali, V.; Salmen, R.; Battelli, L. A.; Dodd, T.; McKinney, W.; Stone, S.; Donlin, M.; Leonard, H. D.; et al. Inhalation of Iron-Abundant Gas Metal Arc Welding-Mild Steel Fume Promotes Lung Tumors in Mice. *Toxicology* 2018, 409, 24–32.
- (37) Liu, Y.; Li, J.; Xu, K.; Gu, J.; Huang, L.; Zhang, L.; Liu, N.; Kong, J.; Xing, M.; Zhang, L.; et al. Characterization of Superparamagnetic Iron Oxide Nanoparticle-Induced Apoptosis in PC12 Cells and Mouse Hippocampus and Striatum. *Toxicol. Lett.* 2018, 292, 151–161.
- (38) Guha, N.; Loomis, D.; Guyton, K. Z.; Grosse, Y.; El Ghissassi, F.; Bouvard, V.; Benbrahim-Tallaa, L.; Vilahur, N.; Muller, K.; Straif, K.; et al. Carcinogenicity of Welding, Molybdenum Trioxide, and Indium Tin Oxide. *Lancet. Oncol.* 2017, 18 (5), 581–582.
- (39) Andujar, P.; Simon-Deckers, A.; Galateau-Sallé, F.; Fayard, B.; Beaune, G.; Clin, B.; Billon-Galland, M.-A.; Durupthy, O.; Pairon, J.-C.; Doucet, J.; et al. Role of Metal Oxide Nanoparticles in Histopathological Changes Observed in the Lung of Welders. Part. *Fibre Toxicol.* 2014, 11, 23.
- (40) Xiong, W.; Wang, L.; Yu, F. Regulation of Cellular Iron Metabolism and Its Implications in Lung Cancer Progression. *Med. Oncol.* 2014, 31 (7), 28.
- (41) Gass, S.; Cohen, J. M.; Pyrgiotakis, G.; Sotiriou, G. A.; Pratsinis, S. E.; Demokritou, P. A Safer Formulation Concept for Flame-Generated Engineered Nanomaterials. *ACS Sustain. Chem. Eng.* 2013, 1 (7), 843–857.
- (42) Sotiriou, G. A.; Watson, C.; Murdaugh, K. M.; Darrah, T. H.; Pyrgiotakis, G.; Elder, A.; Brain, J. D.; Demokritou, P. Engineering Safer-by-Design Silica-Coated ZnO Nanorods with Reduced DNA Damage Potential. *Environ. Sci. Nano* 2014.
- (43) Antonini, J. M.; Lawryk, N. J.; Murthy, G. G.; Brain, J. D. Effect of Welding Fume Solubility on Lung Macrophage Viability and Function in Vitro. *J. Toxicol. Environ. Health. A* 1999, 58 (6), 343–363.

- (44) Sager, T. M.; Porter, D. W.; Robinson, V. A.; Lindsley, W. G.; Schwegler-Berry, D. E.; Castranova, V. Improved Method to Disperse Nanoparticles for in Vitro and in Vivo Investigation of Toxicity. *Nanotoxicology* 2007, 1 (2), 118–129.
- (45) Hackley, V. A.; Stefaniak, A. B. “Real-World” precision, Bias, and between-Laboratory Variation for Surface Area Measurement of a Titanium Dioxide Nanomaterial in Powder Form. *J. Nanoparticle Res.* 2013, 15 (6).
- (46) Cohen, J. M.; Beltran-Huarac, J.; Pyrgiotakis, G.; Demokritou, P. Effective Delivery of Sonication Energy to Fast Settling and Agglomerating Nanomaterial Suspensions for Cellular Studies: Implications for Stability, Particle Kinetics, Dosimetry and Toxicity. *NanoImpact* 2018, 10, 81–86.
- (47) Deloid, G. M.; Cohen, J. M.; Pyrgiotakis, G.; Demokritou, P. Preparation, Characterization, and in Vitro Dosimetry of Dispersed, Engineered Nanomaterials. *Nat. Protoc.* 2017.
- (48) Cohen, J.; DeLoid, G.; Pyrgiotakis, G.; Demokritou, P. Interactions of Engineered Nanomaterials in Physiological Media and Implications for in Vitro Dosimetry. *Nanotoxicology* 2013, 7 (4), 417–431.
- (49) Stefaniak, A. B.; Guilmette, R. A.; Day, G. A.; Hoover, M. D.; Breysse, P. N.; Scripsick, R. C. Characterization of Phagolysosomal Simulant Fluid for Study of Beryllium Aerosol Particle Dissolution. *Toxicol. Vitro.* 2005, 19 (1), 123–134.
- (50) DeLoid, G.; Cohen, J. M.; Darrah, T.; Derk, R.; Rojanasakul, L.; Pyrgiotakis, G.; Wohlleben, W.; Demokritou, P. Estimating the Effective Density of Engineered Nanomaterials for in Vitro Dosimetry. *Nat Commun* 2014, 5, 3514.
- (51) Cohen, J. M.; Teeguarden, J. G.; Demokritou, P. An Integrated Approach for the in Vitro Dosimetry of Engineered Nanomaterials. Part. *Fibre Toxicol.* 2014, 11 (1), 20.
- (52) DeLoid, G. M.; Cohen, J. M.; Pyrgiotakis, G.; Pirela, S. V; Pal, A.; Liu, J.; Srebric, J.; Demokritou, P. Advanced Computational Modeling for in Vitro Nanomaterial Dosimetry. Part. *Fibre Toxicol.* 2015, 12, 32.

- (53) Teeguarden, J. G.; Mikheev, V. B.; Minard, K. R.; Forsythe, W. C.; Wang, W.; Sharma, G.; Karin, N.; Tilton, S. C.; Waters, K. M.; Asgharian, B.; et al. Comparative Iron Oxide Nanoparticle Cellular Dosimetry and Response in Mice by the Inhalation and Liquid Cell Culture Exposure Routes. *Part Fibre Toxicol* 2014, 11, 46.
- (54) Chen, B. T.; Schwegler-Berry, D.; Cumpston, A.; Cumpston, J.; Friend, S.; Stone, S.; Keane, M. Performance of a Scanning Mobility Particle Sizer in Measuring Diverse Types of Airborne Nanoparticles: Multi-Walled Carbon Nanotubes, Welding Fumes, and Titanium Dioxide Spray. *J. Occup. Environ. Hyg.* 2016, 13 (7), 501–518.
- (55) Espósito, B. P.; Epsztejn, S.; Breuer, W.; Cabantchik, Z. I. A Review of Fluorescence Methods for Assessing Labile Iron in Cells and Biological Fluids. *Anal. Biochem.* 2002, 304 (1), 1–18.
- (56) Buss, J. L.; Arduini, E.; Ponka, P. Mobilization of Intracellular Iron by Analogs of Pyridoxal Isonicotinoyl Hydrazone (PIH) Is Determined by the Membrane Permeability of the Iron-Chelator Complexes. *Biochem Pharmacol* 2002, 64 (12), 1689–1701.
- (57) Hanahan, D.; Weinberg, R. A. Hallmarks of Cancer: The Next Generation. *Cell* 2011, 144 (5), 646–674.
- (58) Horibata, S.; Vo, T. V.; Subramanian, V.; Thompson, P. R.; Coonrod, S. A. Utilization of the Soft Agar Colony Formation Assay to Identify Inhibitors of Tumorigenicity in Breast Cancer Cells. *J. Vis. Exp.* 2015, No. 99, e52727.
- (59) O'Connor, M. J. Targeting the DNA Damage Response in Cancer. *Mol. Cell* 2015, 60 (4), 547–560.
- (60) Lorat, Y.; Timm, S.; Jakob, B.; Taucher-Scholz, G.; Rube, C. E. Clustered Double-Strand Breaks in Heterochromatin Perturb DNA Repair after High Linear Energy Transfer Irradiation. *Radiother. Oncol.* 2016, 121 (1), 154–161.
- (61) Nikitaki, Z.; Nikolov, V.; Mavragani, I. V.; Mladenov, E.; Mangelis, A.; Laskaratou, D. A.; Fragkoulis, G. I.; Hellweg, C. E.; Martin, O. A.; Emfietzoglou, D.; et al. Measurement of Complex

DNA Damage Induction and Repair in Human Cellular Systems after Exposure to Ionizing Radiations of Varying Linear Energy Transfer (LET). *Free Radic. Res.* 2016, 50, S64–S78.

(62) Evans, M. D.; Dizdaroglu, M.; Cooke, M. S. Oxidative DNA Damage and Disease: Induction, Repair and Significance. *Mutat. Res. Mutat. Res.* 2004, 567 (1), 1–61.

(63) Stueckle, T. A.; Davidson, D. C.; Derk, R.; Demokritou, P.; Kornberg, T.; Schwegler-Berry, D.; Wang, L. Nano-Ferric Oxide Induced Neoplastic-Like Transformation in a Human Primary Cell Model: Iron Homeostasis Disruption? *Toxicol.* 2016, 2783, 419.

(64) Villeneuve, P. J.; Jerrett, M.; Brenner, D.; Su, J.; Chen, H.; McLaughlin, J. R. A Case-Control Study of Long-Term Exposure to Ambient Volatile Organic Compounds and Lung Cancer in Toronto, Ontario, Canada. *Am. J. Epidemiol.* 2014, 179 (4), 443–451.

(65) Hanahan, D.; Weinberg, R. A. The Hallmarks of Cancer. *Cell* 2000, 100 (1), 57–70.

(66) Wang, Y.; Cui, H.; Zhou, J.; Li, F.; Wang, J.; Chen, M.; Liu, Q. Cytotoxicity, DNA Damage, and Apoptosis Induced by Titanium Dioxide Nanoparticles in Human Non-Small Cell Lung Cancer A549 Cells. *Environ. Sci. Pollut. Res. Int.* 2015, 22 (7), 5519–5530.

(67) Setyawati, M. I.; Sevenscan, C.; Bay, B. H.; Xie, J.; Zhang, Y.; Demokritou, P.; Leong, D. T. Nano-TiO₂ Drives Epithelial–Mesenchymal Transition in Intestinal Epithelial Cancer Cells. *Small* 2018, 14 (30).

(68) Hong, F.; Ji, L.; Zhou, Y.; Wang, L. Chronic Nasal Exposure to Nanoparticulate TiO₂ Causes Pulmonary Tumorigenesis in Male Mice. *Environ. Toxicol.* 2017, 32 (5), 1651–1657.

(69) Donaldson, K.; Schinwald, A.; Murphy, F.; Cho, W. S.; Duffin, R.; Tran, L.; Poland, C. The Biologically Effective Dose in Inhalation Nanotoxicology. *Acc Chem Res* 2013, 46 (3), 723–732.

(70) Galaris, D.; Pantopoulos, K. Oxidative Stress and Iron Homeostasis: Mechanistic and Health Aspects. *Crit Rev Clin Lab Sci* 2008, 45 (1), 1–23.

(71) Tenopoulou, M.; Doulias, P. T.; Barbouti, A.; Brunk, U.; Galaris, D. Role of Compartmentalized Redox-Active Iron in Hydrogen Peroxide-Induced DNA Damage and Apoptosis. *Biochem J* 2005, 387 (Pt 3), 703–710.

- (72) Mesárošová, M.; Kozics, K.; Bábelová, A.; Regendová, E.; Pastorek, M.; Vnuková, D.; Buliaková, B.; Rázga, F.; Gábelová, A. The Role of Reactive Oxygen Species in the Genotoxicity of Surface-Modified Magnetite Nanoparticles. *Toxicol. Lett.* 2014, 226 (3), 303–313.
- (73) Kamiyama, T.; Miyakawa, H.; Jing Ping Li; Akiba, T.; Liu, J.; Liu, J. H.; Marumo, F.; Sato, C. Effects of One-Year Cadmium Exposure on Livers and Kidneys and Their Relation to Glutathione Levels. *Res. Commun. Mol. Pathol. Pharmacol.* 1995, 88 (2), 177–186.
- (74) Prozialeck, W. C.; Vaidya, V. S.; Liu, J.; Waalkes, M. P.; Edwards, J. R.; Lamar, P. C.; Bernard, A. M.; Dumont, X.; Bonventre, J. V. Kidney Injury Molecule-1 Is an Early Biomarker of Cadmium Nephrotoxicity. *Kidney Int.* 2007, 28 (5), 478–485.
- (75) Liu, J.; Qu, W.; Kadiiska, M. B. Role of Oxidative Stress in Cadmium Toxicity and Carcinogenesis. *Toxicol. Appl. Pharmacol.* 2009, 238 (3), 209–214.
- (76) Chang, Q.; Pan, J.; Wang, X.; Zhang, Z.; Chen, F.; Shi, X. Reduced Reactive Oxygen Species-Generating Capacity Contributes to the Enhanced Cell Growth of Arsenic-Transformed Epithelial Cells. *Cancer Res.* 2010, 70 (12), 5127–5135.
- (77) Shoeb, M.; Kodali, V.; Farris, B.; Bishop, L. M.; Meighan, T.; Salmen, R.; Eye, T.; Roberts, J. R.; Zeidler-Erdely, P.; Erdely, A.; et al. Evaluation of the Molecular Mechanisms Associated with Cytotoxicity and Inflammation after Pulmonary Exposure to Different Metal-Rich Welding Particles. *Nanotoxicology* 2017, 11 (6), 1–12.
- (78) Falcone, L. M.; Zeidler-Erdely, P. C. Unpublished Manuscript.
- (79) Lu, X.; Miousse, I. R.; Pirela, S. V.; Melnyk, S.; Koturbash, I.; Demokritou, P. Short-Term Exposure to Engineered Nanomaterials Affects Cellular Epigenome. *Nanotoxicology* 2015, 10 (2), 1–11.
- (80) Zhang, T.; Qi, Y.; Liao, M.; Xu, M.; Bower, K. A.; Frank, J. A.; Shen, H. M.; Luo, J.; Shi, X.; Chen, G. Autophagy Is a Cell Self-Protective Mechanism against Arsenic-Induced Cell Transformation. *Toxicol Sci* 2012, 130 (2), 298–308.

- (81) Gupta, A. K.; Naregalkar, R. R.; Vaidya, V. D.; Gupta, M. Recent Advances on Surface Engineering of Magnetic Iron Oxide Nanoparticles and Their Biomedical Applications. *Nanomedicine (Lond)* 2007, 2 (1), 23–39.
- (82) Bekaroğlu, M. G.; İşçi, Y.; İşçi, S. Colloidal Properties and in Vitro Evaluation of Hydroxy Ethyl Cellulose Coated Iron Oxide Particles for Targeted Drug Delivery. *Mater. Sci. Eng. C* 2017, 78, 847–853.
- (83) Truzzi, E.; Bongio, C.; Sacchetti, F.; Maretti, E.; Montanari, M.; Iannuccelli, V.; Vismara, E.; Leo, E. Self-Assembled Lipid Nanoparticles for Oral Delivery of Heparin-Coated Iron Oxide Nanoparticles for Theranostic Purposes. *Molecules* 2017, 22 (6), 963.
- (84) Ma, J.; Mercer, R. R.; Barger, M.; Schwegler-Berry, D.; Cohen, J. M.; Demokritou, P.; Castranova, V. Effects of Amorphous Silica Coating on Cerium Oxide Nanoparticles Induced Pulmonary Responses. *Toxicol. Appl. Pharmacol.* 2015, 288 (1), 63–73.
- (85) McKeon, K. D.; Love, B. J. The Presence of Adsorbed Proteins on Particles Increases Aggregated Particle Sedimentation, as Measured by a Light Scattering Technique. *J. Adhes.* 2008, 84 (7), 664–674.
- (86) Davidson, D. C.; Derk, R.; He, X.; Stueckle, T. A.; Cohen, J.; Pirela, S. V.; Demokritou, P.; Rojanasakul, Y.; Wang, L. Direct Stimulation of Human Fibroblasts by nCeO₂ in Vitro Is Attenuated with an Amorphous Silica Coating. *Part Fibre Toxicol* 2016, 13 (1), 23.
- (87) Ma, J. Y.; Zhao, H.; Mercer, R. R.; Barger, M.; Rao, M.; Meighan, T.; Schwegler-Berry, D.; Castranova, V.; Ma, J. K. Cerium Oxide Nanoparticle-Induced Pulmonary Inflammation and Alveolar Macrophage Functional Change in Rats. *Nanotoxicology* 2011, 5 (3), 312–325.
- (88) Konduru, N. V.; Jimenez, R. J.; Swami, A.; Friend, S.; Castranova, V.; Demokritou, P.; Brain, J. D.; Molina, R. M. Silica Coating Influences the Corona and Biokinetics of Cerium Oxide Nanoparticles. *Part Fibre Toxicol.* 2015, 12 (1).
- (89) Konduru, N. V.; Murdaugh, K. M.; Sotiriou, G. A.; Donaghey, T. C.; Demokritou, P.; Brain, J. D.; Molina, R. M. Bioavailability, Distribution and Clearance of Tracheally-Instilled and Gavigated Uncoated or Silica-Coated Zinc Oxide Nanoparticles. *Part. Fibre Toxicol.* 2014, 11 (1).

(90) Demokritou, P.; Gass, S.; Pyrgiotakis, G.; Cohen, J. M.; Goldsmith, W.; McKinney, W.; Frazer, D.; Ma, J.; Schwegler-Berry, D.; Brain, J.; et al. An in Vivo and in Vitro Toxicological Characterisation of Realistic Nanoscale CeO₂ Inhalation Exposures. *Nanotoxicology* 2013, 7 (8), 1338–1350.