2019 NanoEHS Webinar Series

Evaluating Worker and Consumer Exposure to Engineered Nanomaterials

October 8, 2019

Presenters

Joanna Matheson, Consumer Products Safety Commission (CPSC)

Paul Schulte, National Institute for Occupational Safety and Health (NIOSH)

Moderated by John Howard, NIOSH

Webinar viewers will be able to submit questions for the panelists to answer during the Q&A period. Submitted questions will be considered in the order received and may be posted on the NNI website. The moderator will identify relevant questions and pose them to the speakers. Due to time constraints, some questions may be grouped and some may not be addressed during the webinar.

>> John Howard: Good afternoon, everyone. Thank you for joining today's webinar, "Evaluating Worker and Consumer Exposure to Engineered Nanomaterials." My name is John Howard. I have the pleasure of introducing our two speakers and moderating the discussion afterwards. Our presenters today are Dr. Joanna Matheson from the Consumer Products Safety Commission, the CPSC, and Dr. Paul Schulte from the National Institute for Occupational Safety and Health, or NIOSH.

Dr. Matheson, a toxicologist with CPSC's Health Sciences Directorate, is the program manager for the agency's nanotechnology program. Her work focuses on risk assessments related to toxic exposure for consumer products, particularly to susceptible populations. Dr. Matheson's research interests relate to the roles of immune and inflammatory mediators and occupationally induced diseases. Dr. Matheson serves as the agency liaison to several Federal interagency committees, and she chairs the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Skin Sensitization Expert Group.

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>> John Howard: Dr. Paul Schulte directs NIOSH's Division of Science Integration and oversees the agency's public health approach to developing and transferring information to prevent occupational injuries and diseases. Dr. Schulte co-manages the NIOSH Nanotechnology Research Center. Dr. Schulte has developed frameworks in areas such as the aging workforce, the burden of occupational disease and injury, well-being of the workforce, and synthetic biology and occupational risk. He is a Fellow of the American College of Epidemiology, with training in toxicology and genetics.

We have budgeted time for your questions for Paul and Joanna; you can type your questions into the "submit your question" box. We will try to get through as many of them as we can.

Before I turn it over to Joanna, I'd like to remind you to please check nano.gov for more information on upcoming webinars. You can also follow us on twitter, @NNInanonews.

So without further ado, Dr. Matheson.

>> Joanna Matheson: Thank you, John.

I'm going to start off briefly introducing you to our agency.

>> Joanna Matheson: Some may not be familiar with the Consumer Product Safety Commission. It was created in 1973. It is an independent Federal Government agency. We are a commission, we are small.

CPSC Overview Jurisdiction

- 5 Commissioners appointed by the President
- FY2019 Budget of $ 126M; staff 545
- Jurisdiction: Products in home, schools, and recreational settings
- Excludes products covered by other federal agencies, such as:
  - Cars and related equipment (NHTSA)
  - Food (USDA and FDA)
  - Drugs, medical devices, cosmetics (FDA)
  - Firearms (ATF)
  - Airplanes (FAA)
  - Boats (Coast Guard)
  - Pesticides (EPA)
  - Tobacco Products (FDA)

>> Joanna Matheson: The commissioners are appointed by the President. We are tasked with jurisdiction of over 15,000 different types of products, with the exclusion of ones covered by other Federal agencies.

However, as demonstrated in the following slides that will focus on all our nano interagency collaborations, the jurisdictions can overlap. And that may be from one considering the life cycle of a consumer product – a nano-enabled consumer product – or for some of the other products, it's because the exposures to such products are common to both consumers and workers.

Federal Hazardous Substances Act (FHSA)

- Risk-based
- Considers toxicity, exposure, and bioavailability
- Includes acute and chronic effects
- Does not require specific testing for chronic hazards
- Does not provide for pre-market approval
- Requires manufacturers to ensure that their products are not hazardous or are properly labeled
- Includes reasonably foreseeable misuse
- Includes mouthing by children

>> Joanna Matheson: One of our overarching acts and particularly as it relates to chemical hazards, is the Federal Hazardous Substances Act, FHSA. This is a self-administering statute, which means that it requires manufacturers to ensure that their products are not hazardous and are properly labeled.

What's important is the agency does not have premarket approval. Therefore, we do not see a product before it is put out onto the market. And we do not require reporting unless the product has caused injuries.

Identified Data Needs for Nano-enabled Product Exposure

- Determination of consumer products that contain nanomaterials and the specific nanomaterials that are incorporated into these products.
- Development of robust analytical methods available to characterize and quantify nanomaterials in various product matrices
- Availability of exposure studies that quantify the release of nanomaterials from products in a variety of media including air and liquids (*e.g.*, surrogate sweat and saliva)
- Development of approaches for estimating human exposure and uptake of released nanomaterials (*e.g.*, nanomaterial-specific exposure models)

>> Joanna Matheson: The CPSC nanotechnology program began in earnest in 2011, but it actually started to perform some interagency collaborations in 2007. And that really was driven by these data needs. It's through these collaborations that we're working to address these needs.

You'll see this common theme with some later slides is (1), it's using the information that's publicly available to determine how many products are out there that may be nano-enabled, and (2) particularly, the development of analytical methods in order to be able to assess the exposure to nanomaterials in consumer products.

These interagency agreements have been with Federal partners, such as DOD, EPA, FDA, NIST, NIOSH, NLM (National Library of Medicine), of course NNCO, and NSF. We've also had academia, such as Duke University, Harvard, Rutgers University, University of Cincinnati, University of Florida, Virginia Tech. And also contract companies, particularly, have assisted us with literature searches on toxicity of nanomaterials of interest—for example, Versar Inc. and the University of Cincinnati's TERA (Toxicology Excellence for Risk Assessment) Center.

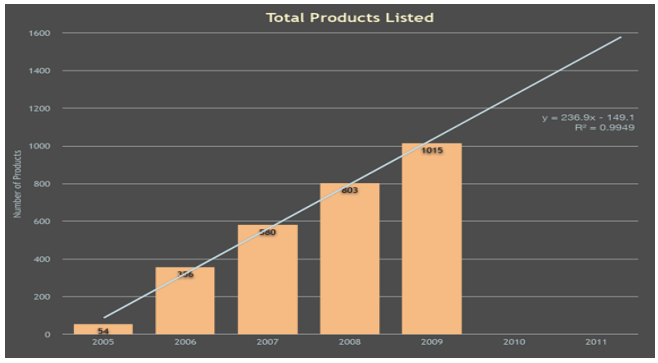
There's been some work with ILSI (International Life Sciences Institute) on the NanoRelease Project, which has already been submitted to the ISO Technical Committee 229.

One of our goals, also, is to try to put some of these methods that have been developed into the voluntary standards process.

Woodrow Wilson Center (WWC)

Report on Nanotechnology and CPSC

WWC database of nano-enabled products



Courtesy of the Woodrow Wilson Center Project on Emerging Nanotechnologies (August, 2008)

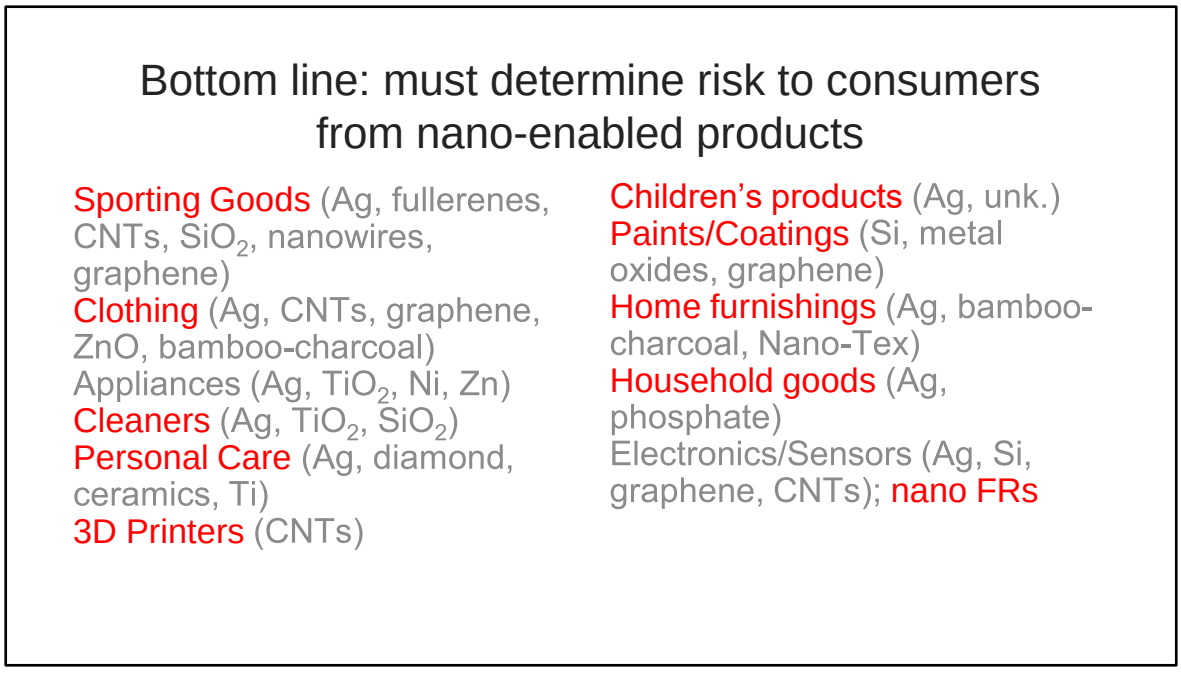
Consumer Product Inventory: http://www.nanotechproject.org/inventories/
Denmark database: http://nanodb.dk/en/
ECHA's: https://nanodata.echa.europa.eu/index.php?r=product%2Fby-country
Netherlands (RIVM): https://www.rivm.nl/en/nanotechnology/consumer-products

>> Joanna Matheson: So, this first thing is, actually how many products are out there, consumer products, that might contain nanomaterials? This is a tough question because products can be labeled that they may have nanomaterials in them, and it turns out that some may not.

One of the earliest inventories was by the Woodrow Wilson Center, which is now called the Nanotechnology Consumer Product Inventory, with Virginia Tech's Matt Hull's group overseeing. This slide is a little outdated, but this demonstrated that there were about 1800 products reported that may be nano-enabled.

There are other databases out there, this is not necessarily a comprehensive list. But one of the more current ones is the Denmark database, which I have a link to here. ECHA (the European Chemicals Agency) also has access to products that may contain nanomaterials. And then the Dutch National Institute for Public Health and the Environment (RIVM) reported some indices.

We had some part-time interns update our consumer inventory, taking materials from the Denmark databases. We actually have in our database about 2800 products, and the reason is, the definition of a consumer product in Europe is little bit different. We do not have jurisdiction over cosmetics, so we've actually -- our summer interns -- screened some of those products out.



>> Joanna Matheson: Why are we interested in this? Market growth is expected to reach $55 billion in 2022, possibly $173 billion in 2025, and this is for consumer products containing nanomaterials. The greatest growth is considered to be consumer applications and particularly electronics.

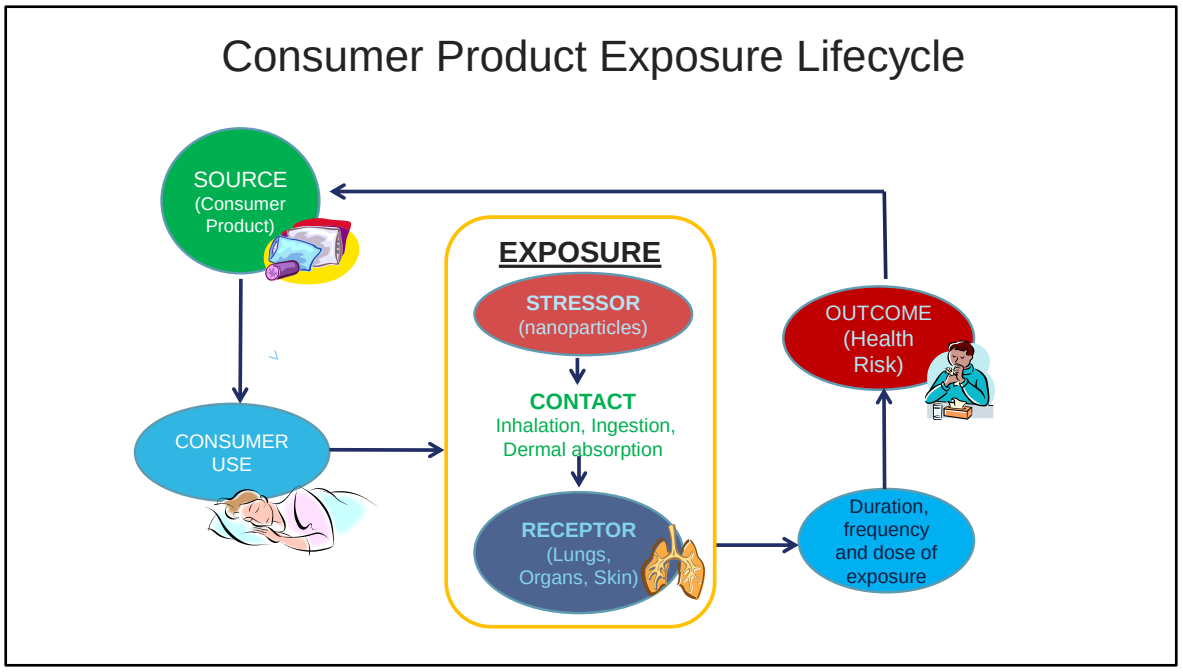
One of the things we've done, too, is to help define where we need to focus our program. What are the materials, and what kind of growth is going to be in those materials? Some of the literature searches we've had from our consulting companies have looked at sample patents. For example, from the period 2013 to 2017, there were 48,000 patents for graphene.

So the bottom line is, we need to determine what the risk to consumers is from those nano-enabled materials/products.

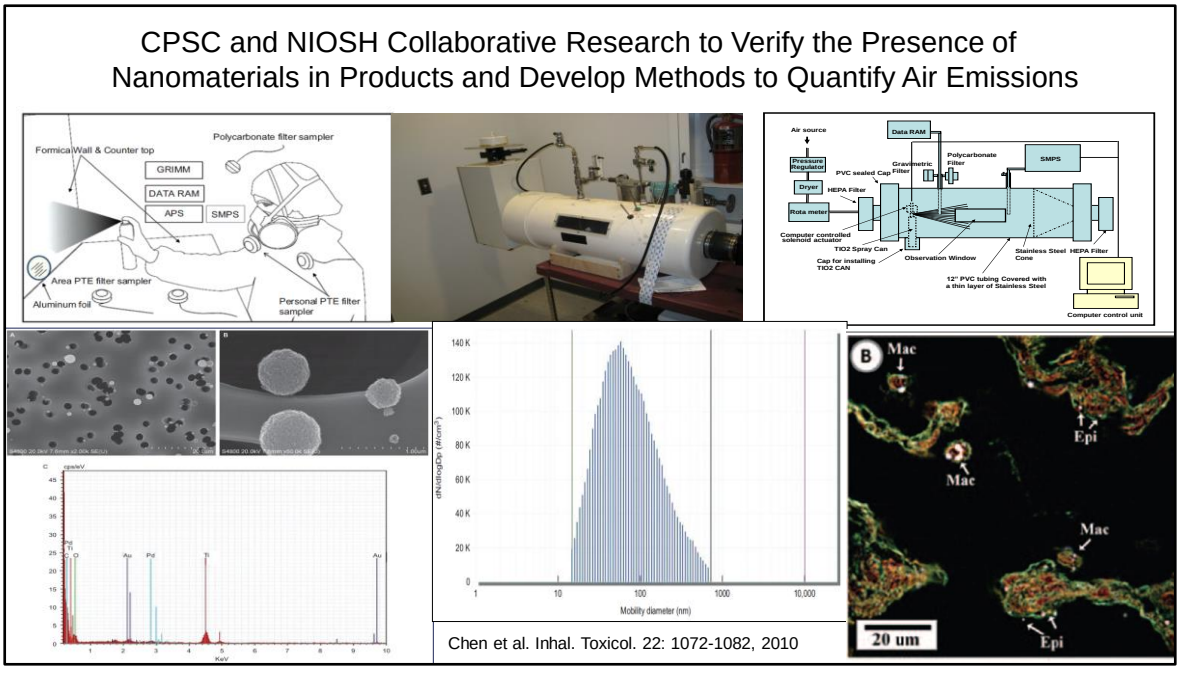
This highlights some of the major groups of products that are reported to have nanomaterials; again, that has to be confirmed. Those highlighted in red are highlighting the categories that CPSC interagency agreements have worked on.

Again, nanomaterials have different electrical, optical, magnetic properties. This is why they are appearing in products: they are providing greater UV protection, repellency, increased antibacterial activity, catalytic ability, strength, resilience.

And so what we've seen with the inventory that our interns updated this summer is about 60% of the products are in clothing, 13% in coatings, paints, sealants—this is what's been seen in the past—13% in tools, and, for example, 10% in sports and other equipment.



>> Joanna Matheson: We are interested in three major routes of exposure to consumers—again, this is going to be common also to workers: inhalation, ingestion, and dermal absorption. We are going to select for consumer use for these.



>> Joanna Matheson: This slide, it's got a lot on it, is summarizing a tremendous amount of work that has had multiple publications.

This was actually one of the first studies that CPSC did in collaboration with NIOSH. One was this method development, being able to collect and characterize nanomaterials that are released into the air; this project was on spray products. This particular one, some of the earliest publications were just describing the system, i.e., the platform that was developed.

For example, here the operator is about 24 inches from the wall, a spray can is held 8 inches from the wall, and the idea is to have systems that reflect realistic exposure conditions.

This work was done with Vince Castranova's group at NIOSH; Chen et al. are the authors of several of these publications.

What was seen from this particular nanospray was that *total particles* released were 1.6 x 10^5 particles per cubic centimeter, with a median diameter count of 75 nanometers—so well within the nanomaterial size range—and *nanoparticles* were about 1.2 x 10^5.

Inhalation Exposure of Rats to Nano TiO_2-Enabled Antimicrobial Spray Aerosol

- From exposure measurements during application, human alveolar burden would be 0.075 µg TiO_2/m^2 of alveolar epithelium/minute = 0.03 µg/rat lung/minute.
- Rat alveolar depositions were 3.74 µg, 9.83 µg, and 43.31 µg; these lung burdens would be achieved in 2, 5 ½ , and 24 hours of application, respectively.
- Conclusion: expected consumer use would result in an alveolar lung burden below the NOEL in this rat study.

McKinney et al. Inhal. Toxicol. 24:447-457, 2012

>> Joanna Matheson: Follow-on work demonstrated that there was pulmonary deposition of the nano-TiO_2-enabled spray.

And following work, which was published in 2012, demonstrated that there was potential for particles in the breathing zone.

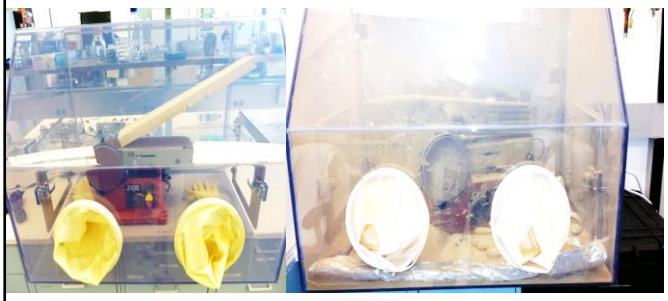
This exposure was carried out for low, medium, and high lung burdens. So, for example, at 2.62 mg per cubic meter, the rats were exposed for 2 hours. The medium range was 4 hours per day for 2 days for a little bit lower amounts. And the higher burden was 3.79 mg per cubic meter for 4 hours per day for 4 days.

The responses were monitored 24 hours post-exposure.

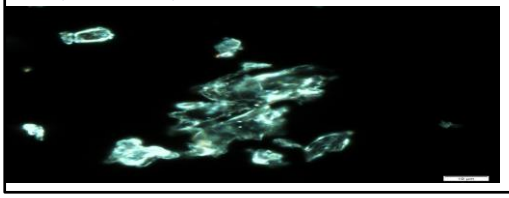
No effects were seen at the low and medium doses, but at the high dose, there was increase in breathing rate, airway resistance, and inflammation and lung damage.

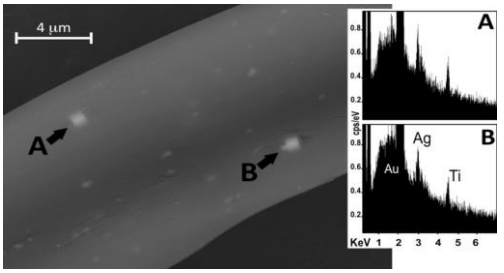
Therefore, it was concluded that for consumer use there would be – would result in – a lung burden well below the NOEL (no observable effect level) from this rat study. Something we've done in our tox literature reviews is determine if the data is robust enough, can a NOEL or LOEL (lowest-observed-effect-level) or even an ADI (Acceptable Daily Intake) be calculated from the data that is available?

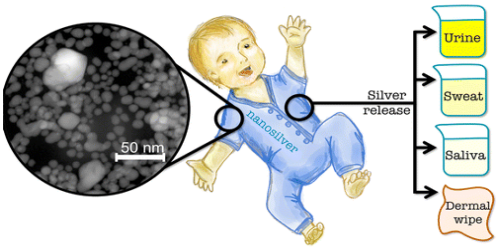
Nanoparticle Concentrations in Various Matrices and Children's Products



Wood Dust Generation (Sanding Dust)
A belt disc sander (Skil, model 3376-01, 4"×36") with 240 grit aluminum oxide sanding belt (Powertec, 110200) was installed in a closed glove box (Cleatech LLC, 2100-2-B, 35"W × 24"D × 25"H). Wood dust was generated and dusts around the sander were collected for animal exposure.
J Sisler, A Hecht et al., CPSC and NIOSH







Silver particles (A and B) inside polyester fibers observed in backscattered mode by SEM (left) and EDS spectra from particles A and B (right)
M Vance et al., 2013 UVA (CPSC and EPA)

>> Joanna Matheson: This next slide is showing several studies, looking at the nanoparticles released in various matrices in children's products. This is the result of multiple interagency collaborations.

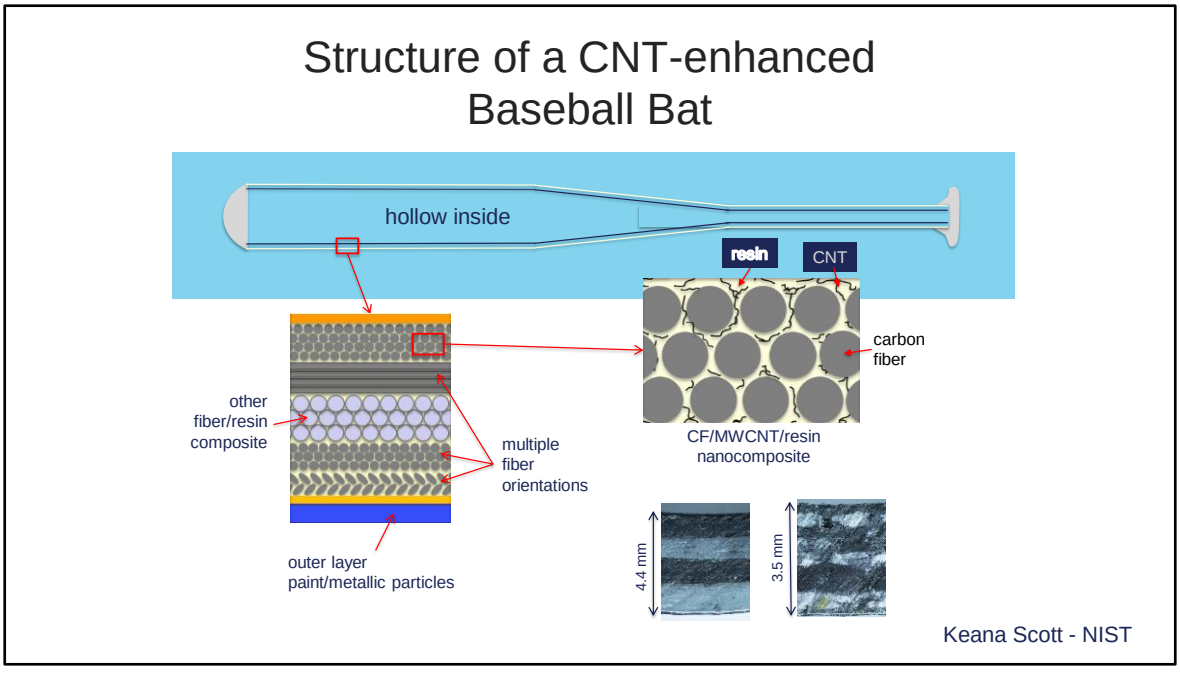
On the right is some of the data looking at the release of several silver nanoparticles from multiple products. This is with the EPA. They looked at 60 products. The vast majority of them, actually, did not contain silver nanoparticles. The ones that were positive were a children's plush toy, a blanket, and also a cleaning spray.

They looked at the various types of matrices, body fluids, to see whether the nanomaterials would leach out. So, for example, synthetic sweat and urine leached the most silver, ranging from, depending on the product, 6 to 38%. It was primarily in the ionic form, so therefore, dissolution was the expected mechanism. Water leached the least.

There was actually no trend between aging and leaching. This is something we do with some of the other studies, too, because this is a reasonable use, to look at aging, whether it's through UV exposure, temperature, etc., to a consumer product.

Dermal transfer is expected to be low. Here, children's exposures were expected to be low, and again here, the bioavailable silver is ionized and not in particulate form.

On the left, some NIOSH studies were looking at the generation of wood dust and the presence of nanomaterials in that dust, because, again, nanomaterials can be used with wood treatment products. There are actually several papers that have been published on that (which I will get to later on).



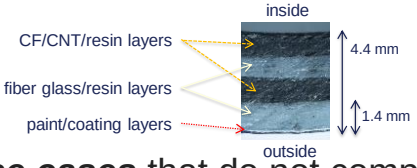
>> Joanna Matheson: As we mentioned earlier, there are nanomaterials used in a large number of sporting equipment types, so this is work performed by Keana Scott at NIST.

What she looked for using various analytical microscopy methods, like SEM (scanning electron microscopy), TEM (transmission electron microscopy), and Raman (just to see where the nanomaterial was in the product) – and then used SEM and TEM to address where/if nanomaterials were being released from the products.

As you can see from this figure, the bats have multiple layers of a composite material. The carbon nanotubes are fairly far below the surface of the bat, about 0.1 millimeter.

Normal Use Cases

Flexing and bending
CNT containing nanocomposite layers are *NOT* on the bat surface



Normal use cases that do not compromise the surface layer/coating **should not result in CNT release**

>> Joanna Matheson: What she saw with these studies is that the incidental release, so just normal wear and use, did not result in release of the carbon nanotubes.

One of the things they also did was simulate the release, for example, if the bat was broken; this was done by sawing and cutting the bat. This did result in release of nanosized particles – multiple carbon nanotubes in resin. At the time, they were not able to quantitate how much was being released.

This has been an issue with multiwall carbon nanotubes; it has been a challenge to be able to quantitate release from products.

Release Pathways of Nanocomposite Nanoparticles

Goal:

- Develop test methods and measurement protocols for determining the quantities and properties of particles released from nanoparticle-engineered consumer products
- Understand the mechanism that causes nanoparticle release during exposures to the environments

Mechanical abrasion#

Polyurethane (PU) flooring coatings on wood substrates

- SiO_2
- Al_2O_3

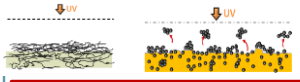
Latex Coatings on a dry-wall substrate

- **TiO_2**
- ZnO
- Ag

Matrix Degradation via UV

Model Epoxy (EP)

- MWCNT
- SiO_2



Exterior Coatings and Paints

- **SiO_2-PU**
- ZnO -Latex

***Abrasion after UV exposure**

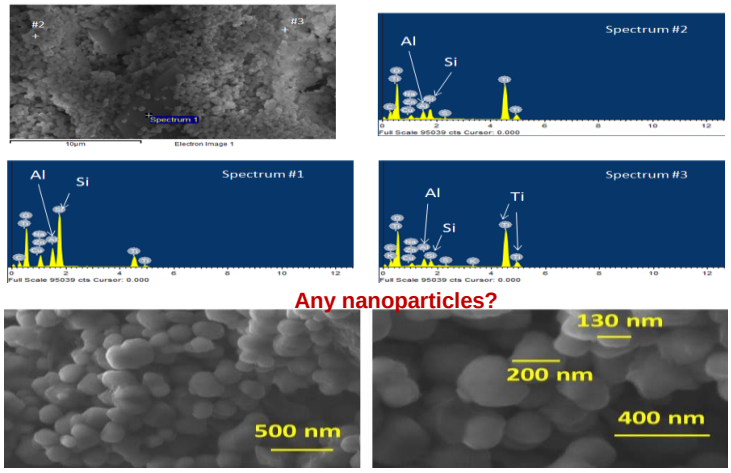
#Airborne release particles- *working with Indoor Air Quality Group/EL*

Li Piin Sung et al., NIST

>> Joanna Matheson: This is another project, an interagency agreement that occurred with NIST, with Li-Piin Sung. This work looked at the influence of UV and mechanical abrasion on release of nanocomposites, nanoparticles, from flooring and flooring-coating treatments.

Quantifying released particles collected from residues from abrasion wheels

EDS spectrum on nanopaints (NP) residues obtained after TGA measurement



Li Piin Sung et al., NIST

>> Joanna Matheson: Again, this was more about method development and looking at the differences between the different blades that are used for abrading these materials.

One of the things they noticed is that the wheels -- the different types of abrasion wheels themselves -- were releasing nanoparticles, and it was not coming from the materials themselves.

And so we're hoping that some of this work could be incorporated into a voluntary standard so that there are set standards and that some of these best practices can be communicated, particularly, to manufacturers and to the larger group.

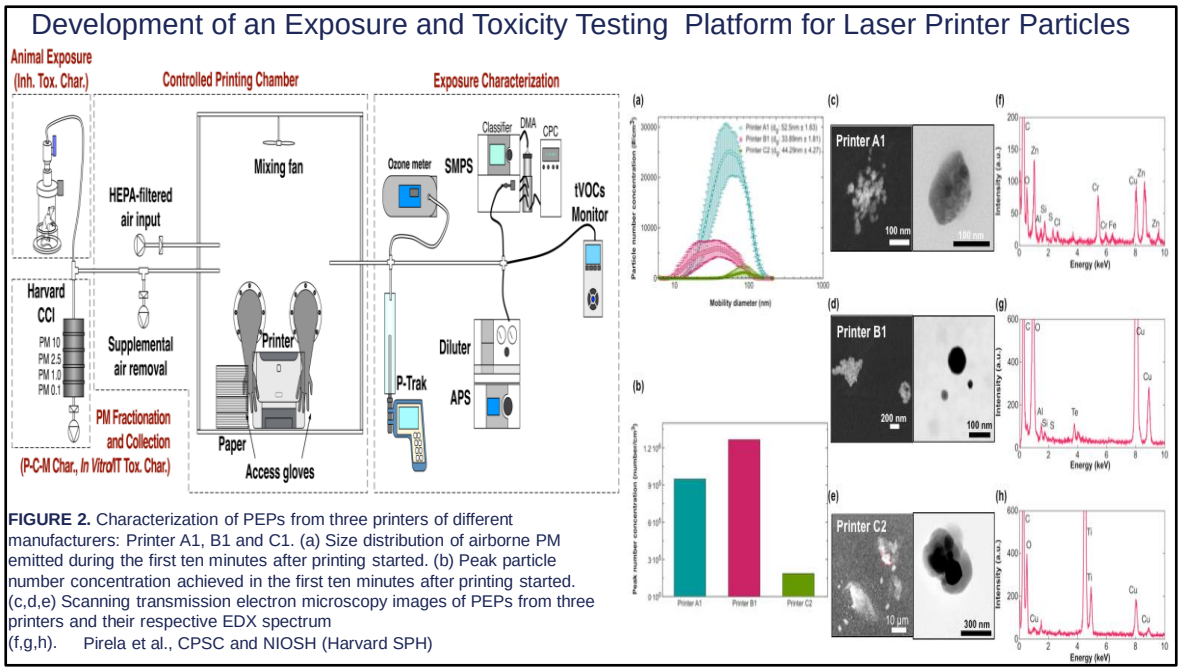


FIGURE 2. Characterization of PEPs from three printers of different manufacturers: Printer A1, B1 and C1. (a) Size distribution of airborne PM emitted during the first ten minutes after printing started. (b) Peak particle number concentration achieved in the first ten minutes after printing started. (c,d,e) Scanning transmission electron microscopy images of PEPs from three printers and their respective EDX spectrum (f,g,h). Pirela et al., CPSC and NIOSH (Harvard SPH)

>> Joanna Matheson: This next slide is actually from a large body of studies.

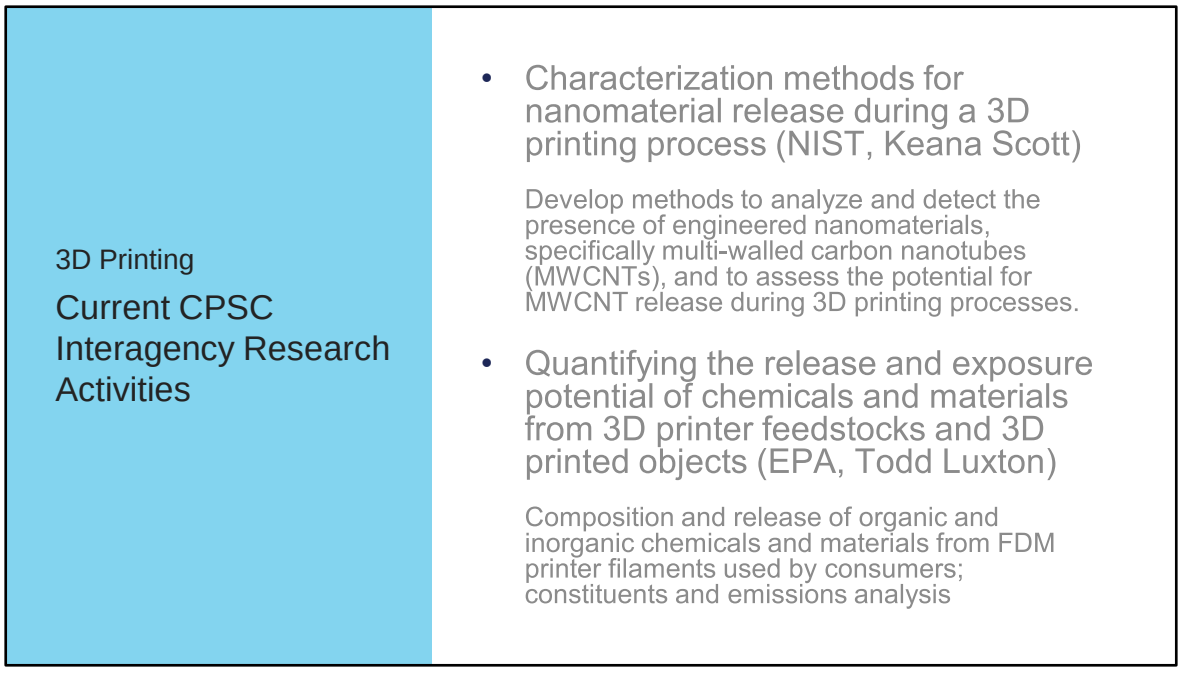
This is probably one of the most robust interagency agreements, again with NIOSH, and also with Harvard University.

Sandra Pirela is the author on some of these papers, there's Dr. Lu, and also from Vince Castranova's group, continued by Yong Qian at NIOSH. If you attended the 2nd Quantifying Exposure to Engineered Nanomaterials (QEEN II) conference workshop that we had last year [2018], Sandra Pirela presented some of this work. This provides a great platform of showing a tiered strategy for assessing the release of nanomaterials.

Laser printers are emitting more than just nanomaterials, this is showing a mixed exposure. This started off by characterizing seven printer systems for being able to assess the exposure and the release of products from laser printers. It then progressed to *in vitro* studies, and then to *in vivo* studies. There have been at least seven different papers published, and there are more to come. Some of the newer papers will be on the cardiovascular effects.

This work demonstrated that laser printers released up to a million particles per cubic centimeter – most of them nano in size. The exposure was a mixture: it was carbon, it was metal, metal oxides, PAHs (polycyclic aromatic hydrocarbons), ozone, and carbon dioxide.

There was consistent reporting that both the *in vitro* and *in vivo* studies saw effects on immune responses, gene expression changes, and these were all tailored to be realistic exposure scenarios.

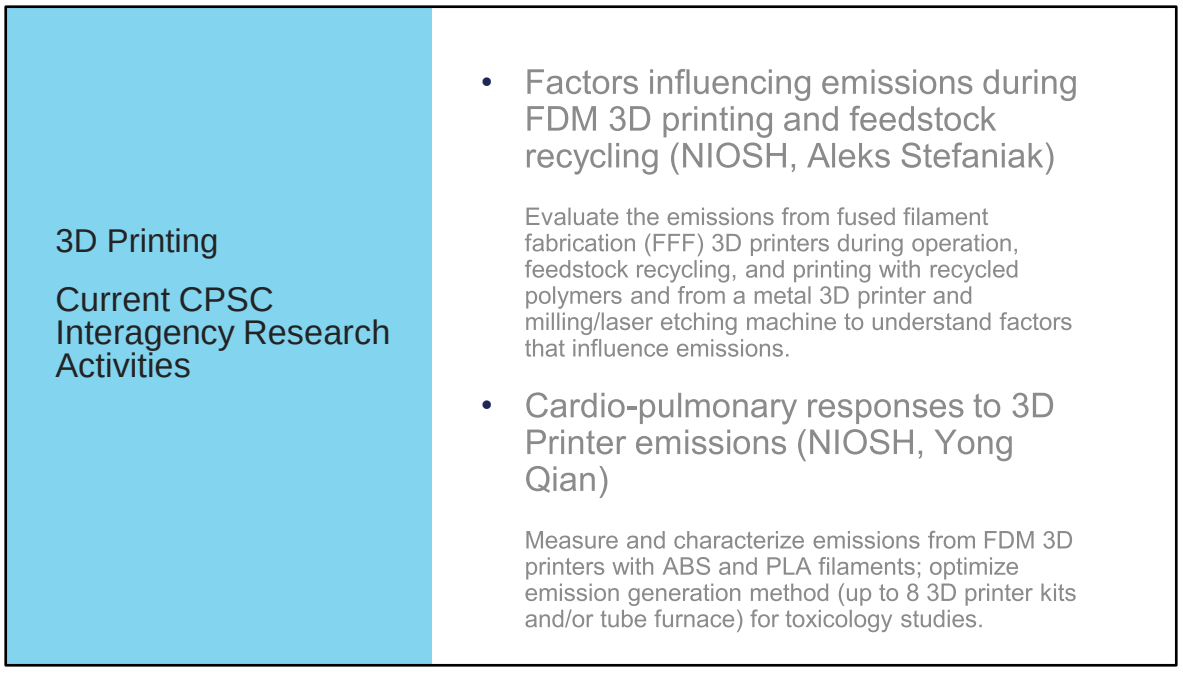


>> Joanna Matheson: Some of our current work is focusing on 3D printing. This is an emerging issue. You'll see this concern is for consumers because you can have at-home use of 3D printing. There are now more than 600 -- I think 600 different types of 3D printers available to consumers. They are very affordable.

And it's not just in the home; they are used in schools, and in libraries. And their use is -- their value is expected to exceed $30 billion by 2022.

Adult hobbyists and home-based manufacturers account for a lot of the home use, but again, some of these are being marketed for use by children, and that's why some school districts have been very concerned.

There are a broad range of filaments available.



>> Joanna Matheson: Our current work with these interagency agreements have been focused on the most common filaments, ABS (acrylonitrile butadiene styrene) and PLA (polylactic acid).

The other thing, which one of the next slides will address, is that consumers can make their own filaments, and these are using blended or recycled materials. These recycling equipment are cheap, available for only a couple of hundred dollars.

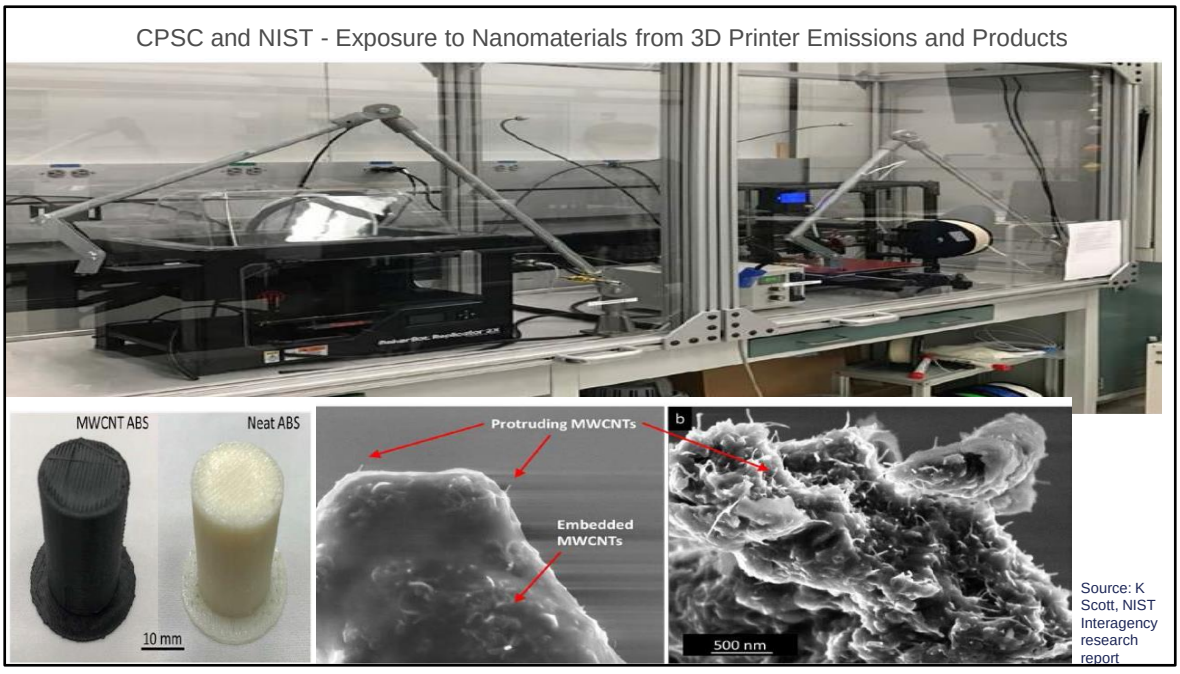
I'll show you some of the slides from Keana Scott's NIST work, where she's been working on developing methods to analyze and detect the presence of carbon nanotubes in 3D filaments – some of filaments can contain carbon nanotubes. And then some of the work that Todd Luxton is doing.

This interagency work is among the agencies we're coordinating with, between EPA, two investigators at NIOSH, and also with NIST.

Aleks Stefaniak is leading the work on looking at the influence of the device, four different printers, looking at the extruder, also looking at the feedstock, looking at six different types of plastic: Does the composition of the plastic make a difference? Is virgin versus recycled plastic affecting the emissions?

Dr. Yong Qian's lab is looking at the toxicity side of this.

And Todd Luxton's group at EPA in Cincinnati is doing characterization of the materials within the filament and also what's being released from it.

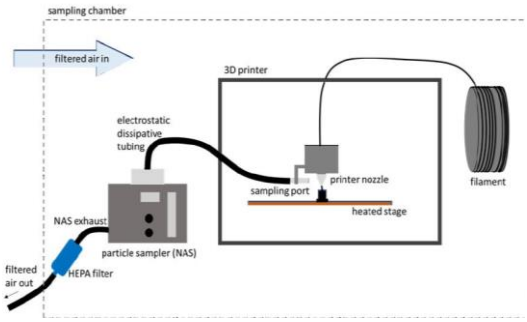


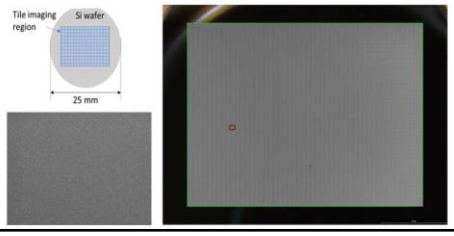
>> Joanna Matheson: CPSC had a poster presented at the SOT (Society of Toxicology) 2017 meeting, two years ago now, that was on already published information. Kent Carlson and a summer intern Samantha Jackson prepared that poster. That was based on data from a 2016 publication. That poster focused on the VOCs (volatile organic compounds) emitted from 3D printers and whether those emissions exceeded non-cancer, acute, or chronic tox reference values.

They used a one-zone model and looked at the influence of air exchange rates. What they saw was a ventilation rate that was above the ASHRAE minimum standard mitigated most of the risk from the emitted VOCs.

The next couple of slides are from Keana Scott's work where she has set up multiple printers, looking at the influence of being able to adjust the sample port positions for air sampling, and neat versus multiwalled carbon nanotube ABS filaments. The ABS filaments are about 5% by weight multiwalled carbon nanotubes, and the size is about 30 mm tall by 22 mm wide.

What she is seeing is that many of the particles (this picture I don't have) have a twisted morphology; multiwalled carbon nanotubes are embedded and protruding from the emitted particles.



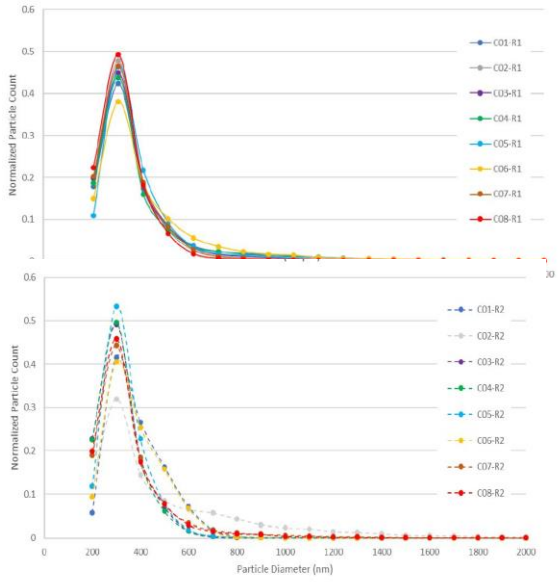


Sampling Design for 3D Printer Emissions

- 2 3D printer models
- Five factors were examined in study and ranked by impact
  1. Sampling port distance from extrusion nozzle
  2. Printer model
  3. Filament type
  4. Filament storage condition
  5. Extrusion temperature
- Sampling
  64 silicon wafers; 32 printing runs; 8 blank runs analyzed by SEM

Electrostatic precipitator and silicon wafer
Source: K Scott, NIST Interagency research report

>> Joanna Matheson: This next slide is demonstrating some of the different factors that she was looking at in different models: the port distance, which made a difference; the printer model; filament type; filament storage condition; and extrusion temperature.



MWCNT Release and Particle Morphology

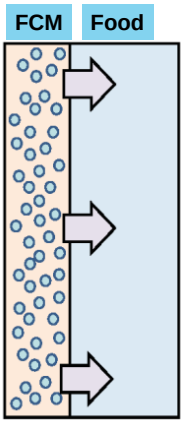
- SEM imaging
- 100,00 images collected
- Identifies range of particles from ABS filament
  Presence of CNT caused variation in size and morphology of particles
- Neat ABS has higher particle number density
- MWCNT maintaining matrix integrity?
- No individual MWCNT's found

Comparison of 3D printer models by particle size and count
Source: K Scott, NIST Interagency research report

>> Joanna Matheson: In addition, she is looking at the morphology. Essentially the bottom line is, no individual multiwalled carbon nanotubes were found. Fewer particles were collected when printing with the neat ABS filament.

Current work, she's now looking at long-term emissions from 3D printers.

Migration from Food Contact Materials (FDA – CFSAN)



Safety depends on:

1) Toxicity: are migrants harmful to health?

2) Exposure: can nanoparticles migrate into foods?

- Diffusion of Engineered Nano Products (ENPs) through plastics
- Partitioning of ENPs into food matrix
- Post diffusion processes

Migration measurements under Condition of Use

Single Use

Repeat Use Room Temp.

Repeat Use High Temp.

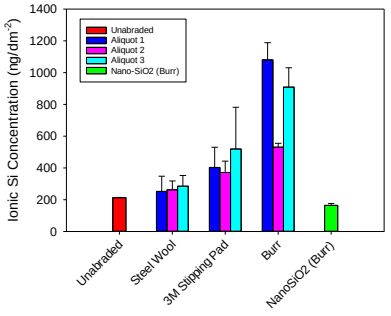
>> Joanna Matheson: These last slides – this is a very brief overview – some long-term collaborations have been with the FDA on migration of nanomaterials from food contact materials.

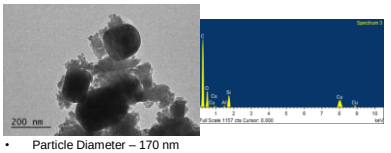
For example, nanomaterials can be in sauce pots, frying pans, cutting boards, and ceramics.

And this was addressing some of the different use scenarios that would release nanomaterials from these products; some of it was just from cutting with a knife.

Migration into 3% acetic acid

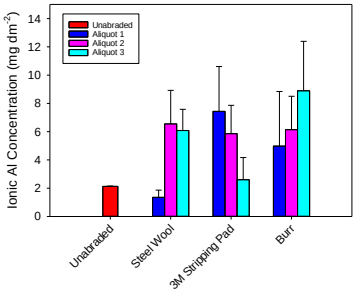
Ceramic-coated Fry Pan



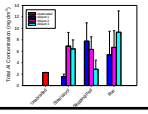


- Particle Diameter – 170 nm
- Particle number - 1.6E+07 p'cles/dm²

Ceramic Sauce Pot



- No nanoparticle migration observed
- Total Aluminum after digestion equal to ionic silver by sp-ICPMS



Addo Ntim et al., 2015

>> Joanna Matheson: This is from Dr. Susana Addo Ntim. She published a couple of papers on this; this was looking at the influence of different food simulants on potential nanoparticle migration.

What we are seeing is that, for example, the aluminum migration was not significantly different between the three abrasion attachments – those were pads, steel wool, and burr – nor for the unabraded pot. Total aluminum after digestion was not statistically different from ionic silver.

This is all done by ICP-MS (inductively coupled plasma mass spectrometry).

Federal Collaborations

- EPA (Todd Luxton): work assessed the release of CuNPs from micronized copper treated lumber; evaluated ENM surface coatings applied to indoor and outdoor surfaces, metal oxides (zinc, cerium)
- DOD (Igor Linkov, Al Kennedy, Taylor Rykroft): Nanoprioritization tool

>> Joanna Matheson: There are some additional collaborations; there isn't time, but I just want to show you some of the publications or reports on it.

Todd Luxton's group at EPA has looked at the release of metal oxides, or micronized copper, from treated lumber – copper nanoparticles release – and then, also, use of nanomaterials in surface coatings, particularly the metal oxides.

They also looked at, for example, the influence of UV and aging on the release.

One of the things, too, the program has worked for is the development of tools. This is highlighted by this interagency work with the DOD ERDC (Engineer Research and Development Center); this is the work of Igor Linkov, Al Kennedy, and Taylor Rycroft. This is the nano prioritization tool.

We use this tool to take a product that we know may contain nanomaterials and put it through this tool. It generates a score based on known information and its default values, so that we can then target the products that may have the highest risk to consumers.

This tool has been submitted and is part of the collection that OECD (Organisation for Economic Co-operation and Development) has on tools and methods.

Another tool we developed, and I don't have a slide on it, but this was working with Andy Persily's group at NIST. It was updating or revising the indoor air CONTAM model so that it was for nanomaterials being released in indoor air.

International Collaborations

- NanoWIR²ES: NanoWire intelligent re-design and recycling for environmental safety; Safe Implementation of Innovative Nanoscience & Nanotechnology (SIINN) program, Chris Volpe, University of Florida.
- Risk Assessment for Manufactured Nanoparticles Used in Consumer Products (RAMNUC), Gedi Mainelis, Rutgers University; assessing inhalation exposure to airborne nanoparticles and their agglomerates from the use of sprays (i.e., nano zinc and silver).


Crumpling versus puncturing: A biomechanical threshold for the acute cellular toxicity of silver nanowires

Characterization of airborne particle release from nanotechnology-enabled clothing products

>> Joanna Matheson: We have several international collaborations. This is through NSF and also from EPA, the nanoWIR²ES is currently ongoing. Chris Volpe's lab at the University of Florida has been working on this. They just published the first article, looking at silver nanowires in touch screens. Part of this work, this is with five labs, international, is not only to look at the release and toxicity but also to work with manufacturers on developing a safer product.

The RAMNUC (Risk Assessment for Manufactured Nanoparticles Used in Consumer Products) was another international collaboration; Gedi Mainelis from Rutgers University participated. It assessed inhalation exposure to airborne nanoparticles and their agglomerates from use of sprays – for example, nano zinc and silver. There have been some publications from that. And he's continued that work with us looking at the release of nanoparticles from consumer sprays. For example, more that five billion nanoparticles per cubic meter can be released. Work that he is finishing up is looking at the deposition of these nanomaterials in house dust, and with the resuspension with walking and with crawling. Again, if you were able to participate at the QEEN II conference last fall, which is what this slide is highlighting, you were able to hear of some of his work.

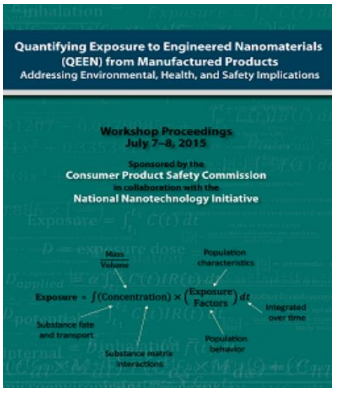
Call to Action for Exposure Science and NanoEHS Communities

QEENI sponsored by CPSC and NNI

- Brought together wide range of stakeholders
- Lifecycle exposures: from production, use and disposal
- Identified exposure methods and approaches for various media
- Demonstrated global efforts for exposure science
- Refined research needs

QEEN II sponsored by CPSC, OSHA and NNI October 9-10, 2018

- Advances and gains since QEENI
- 3D printers; Food Contact; Life Cycle Assessment; Exposures in Agroecosystems, Workplace and to Consumers; Dosimetry Modeling; Metrology



QEEN report released March 28, 2016 on nano.gov

>> Joanna Matheson: There actually have been two QEEN conferences. This was a call to action for exposure science in the general EHS community. The first QEEN conference occurred in 2015; its report was released in 2016, and you can find that on the nano.gov website. It brought together a wide range of stakeholders, demonstrated what's been going on globally, identified needs, and also identified advances. This was repeated at the QEEN II conference last fall (2018) co-sponsored by CSPC, OSHA, and NNI. It demonstrated the gains that had occurred, It also indicated some of the continuing needs, for example, the lack of epidemiology studies – particularly that there are very few on consumer exposures.

QEEN and Collaborative Studies Summary Consumers

- What is released from nano-enabled products is often a mixture of ENMs and other product ingredients, product matrix likely affects ENM emissions
- ENM release levels are expected to be low and exposure scenarios are likely to be chronic
- Systemic consumer exposure to ENMs is dependent on ENMs ability to translocate; translocation is slow so exposure is anticipated to be low over a product's lifetime
- Children have higher exposures per unit body mass to AgNPs in consumer products

>> Joanna Matheson: My second-to-last slide is summarizing some of the discussions from the QEEN conferences.

Really, some of the needs are – as we've been working on from these interagency agreements – is to have realistic exposure assessment. That is a challenge, considering the entire life cycle of a product and the different use scenarios.

One of the things that I somewhat demonstrated that I haven't highlighted too much is the methods that are being used. We're using a lot of intensive methods – SEM, TEM – and there's certainly a need for less expensive and easier-to-use techniques in order to assess exposure.

There also is a lack of nanomaterial biodistribution, bioavailability, biotransformation data, for adverse outcomes in humans, from nanomaterials released from consumer products.

The CPSC has a database called saferproducts.gov, where anybody can report an incident where they feel they have a health effect or concern. It could be from a consumer, it could be from medical staff, it could be from any kind of state official. We've actually received less than a handful of incidents regarding nanomaterials. The bulk of these have actually been complaints about efficacy, which is not actually our jurisdiction.

Thank You!

CPSC Information
- www.cpsc.gov
- www.saferproducts.gov
- CPSC Chemical Hazards webpage: https://www.cpsc.gov/Research--Statistics/Chemicals

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Dr. Justin Gorman, NIST
Dr. Matt Hull, Virginia Tech
Dr. Todd Luxton, EPA
Dr. Sandra Pirela, Harvard SPH
Dr. Yong Qian, NIOSH
Dr. Keana Scott, NIST
Dr. Jennifer Sisler, NIOSH
Dr. Aleks Stefaniak, NIOSH
Dr. Nicolle Tulve, EPA
Dr. Marina Vance, University of Colorado

>> Joanna Matheson: I encourage people to go to our website, www.cpsc.gov. One of the things we want to do is publicize the nanomaterials projects on our chemical hazards webpage. We plan on posting a list of all the technical reports that have been generated from this program, as well as the publications. Right now there's just a couple of reports, the QEEN reports, the nano statement, which has just been updated. But we also plan to start putting up our technical reports, including particularly, a push for the tox ones. There's high interest in that. Stay tuned to our site. If there's something you need, I also have my contact information here.

I have a list of acknowledgments. This is not a complete list, just some of the many people who have been so helpful in our program, starting off with Treye Thomas who has long been the skillful leader in managing our nanotechnology program. We could not have gained this information and this data without assistance from all these agencies and from academia and from the contract labs.

Some of our next steps that we are hoping for, I've already mentioned, are pushing for some of these methods to go into voluntary standards—and some already have. For example, Aleks Stefaniak from NIOSH is leading a project with ASTM International Committee E56 on release of silver materials in textiles, and now there is further work on a work plan on using SEM. And again, we're hoping to propose projects with ISO Technical Committee 229. NanoRelease, which I mentioned earlier has ongoing work there, and we are hoping to propose some of our abrasion studies for a voluntary standard. I thank you, and I'll turn it back over to John.

Evaluation of worker exposure to engineered nanomaterials: taking stock of epidemiological research

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

31

>> John Howard: Thank you, Dr. Matheson. Now we'll hear from Dr. Schulte on worker exposure to engineered nanomaterials.

>> Paul Schulte: Thank you, Dr. Howard. Hello, everybody.

Yes, I'm going to talk about worker exposure. I'm going to talk about the epidemiologic effects, or the adverse health effects, that have been found in the worker populations.

I'd like to acknowledge my colleagues. This work is from a paper that was recently published in the May [2019] issue of the Scandinavian Journal of Work and Environmental Health.

It has been about 20 years since engineered nanomaterials came into commerce.

32

>> Paul Schulte: It's been about 20 years since engineered nanomaterials came into commerce, and so it might be a good time to take stock of what we know about the health effects of people exposed to them.

Workers are generally the first people exposed to any technology. Clearly, in all the products that Joanna was talking about, workers were involved in making those products. And so when we think about trying to figure out what are the health effects in people, as opposed to animals, we have a lot of difficult issues to deal with.

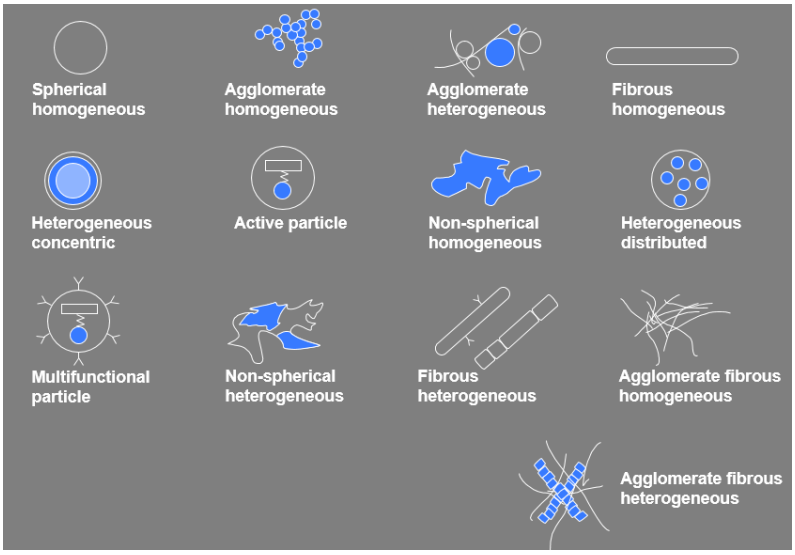
Factors that affect assessment of ENM health effects in workers

- **Immense universe of potentially unique ENMs and great diversity in toxic potential**
- Assumed low extent of exposure due to global attempt to promote responsible development of the technology
- Difficulty assembling study cohorts of similarly exposed workers
- Lack of clarity on appropriate early indicators or biomarker of adverse effects

33

>> Paul Schulte: First of all, there's an immense universe of potentially unique engineered nanomaterials, and they have a range of toxic potential -- all nanoparticles don't have the same toxic potential.

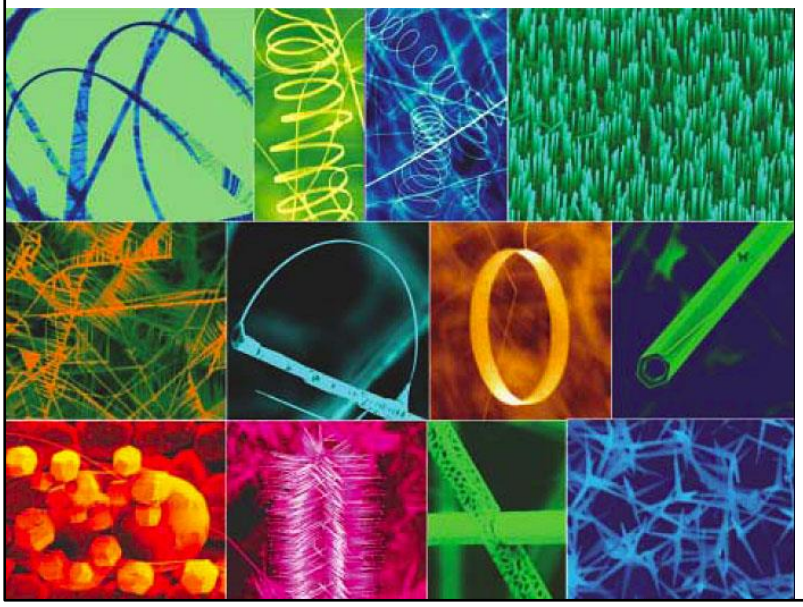
Diversity of Nanomaterials



Source: Schulte, et al. [2009], adapted from Maynard

34

>> Paul Schulte: You can see they have different shapes, different sizes.



Same composition —different shape

Zinc oxide nanoparticles

Source: Materials Today June 2004. Zhong Lin Wang, Georgia Institute of Technology

35

>> Paul Schulte: You can have the situation where you have the same composition but different shapes.

Table II. Properties of interest for nano-object characterisation during risk assessment collected from published literature.

Property	SI units	Frequency(#/28 lists)	List source*
Surface area(specific)	m^2 (m^2/kg, m^2/m^3)	28	a – bb
Elemental/molecular composition (bulk)	mol/mol, kg/kg[+]	27	a – j, l – bb
Surface chemistry	mol/m^2	25	a – f, h, k – bb
Particle size	m	24	a, b, d – l, n – p, s – bb
Particle size distribution	-[‡]	24	b – d, f – w, z – bb
Morphology/shape/form	-[¶,§]	24	a – i, k, l, n – x, z, aa
Surface charge	-[‖]	24	a – h, k – t, v – aa
Agglomeration/aggregation state	-	20	a – g, j, l, m, o – s, w, y, z – bb
Crystal structure	-[&]	17	a, d – f, j, l, n, o, q – t, v, w, z – bb
Surface reactivity	-[#]	16	a – f, l, n – p, r, t, v, w, x, bb
Solubility (water)	mol/l, kg/kg, kg/m^3	14	a, e, h, l – n, p, r, t, v, w, x, z, aa
Dispersibility (dry/wet)	-[ʃ]	13	a, d, e, g, h, l – n, r, t, w, y, aa
Particle concentration[∞]	particles/m^3	8	a, g, h, l, m, p, q, z
Solubility (biological)	-	8	a – c, h, l, n, y, aa
Porosity (specific)	m^3/m^3(m^3/kg)	7	l, n, q – t, z
Stability	-[↕]	6	c, h, m, p, t, v
Density	kg/m^3	4	n, r, t, v
Surface morphology/structure	-	4	e, l, t, w
Conductivity	-[´]	3	l, t, v
Defect density[+]	Defects/m^3, defects/kg	2	l, w
Hardness	-	2	t, v
Magnetic properties	-	2	e, v
Optical properties (refractive index)	1[ſ]	2	t, v

Stefaniak et al. (2013)[36]

>> Paul Schulte: You can have nanomaterials that have a broad range of physical-chemical characteristics. All these factors influence the potential to cause health effects.

Factors that affect assessment of ENM health effects

- Immense universe of potentially unique ENMs and great diversity in toxic potential
- **Assumed low extent of exposure due to global attempt to promote responsible development of the technology**
- Difficulty assembling study cohorts of similarly exposed workers
- Lack of clarity on appropriate early indicators or biomarker of adverse effects

37

>> Paul Schulte: Secondly, nanotechnology came onto the scene at a time when people had a consciousness that they didn't want to see – society didn't want to see – another asbestos, another case where people sat on information about potential hazards.

So right at the beginning of the commercialization of nanotechnology, authoritative groups sent out warnings, sent out caution. They said, "Address the safeguards to workers and consumers. And treat this with caution, because there's the potential for health effects, but we don't know necessarily what the specific health effects are or if they will actually occur."

The Royal Society & Royal Academy of Engineering (2004)

"There are uncertainties about the risk of nanoparticulates currently in production that need to be **addressed immediately to safeguard workers** and consumers and support regulatory decisions."

38

>> Paul Schulte: We're looking at a time when society was trying to be a little more vigilant, and that was passed on, to some extent, to employers, who then instituted controls.

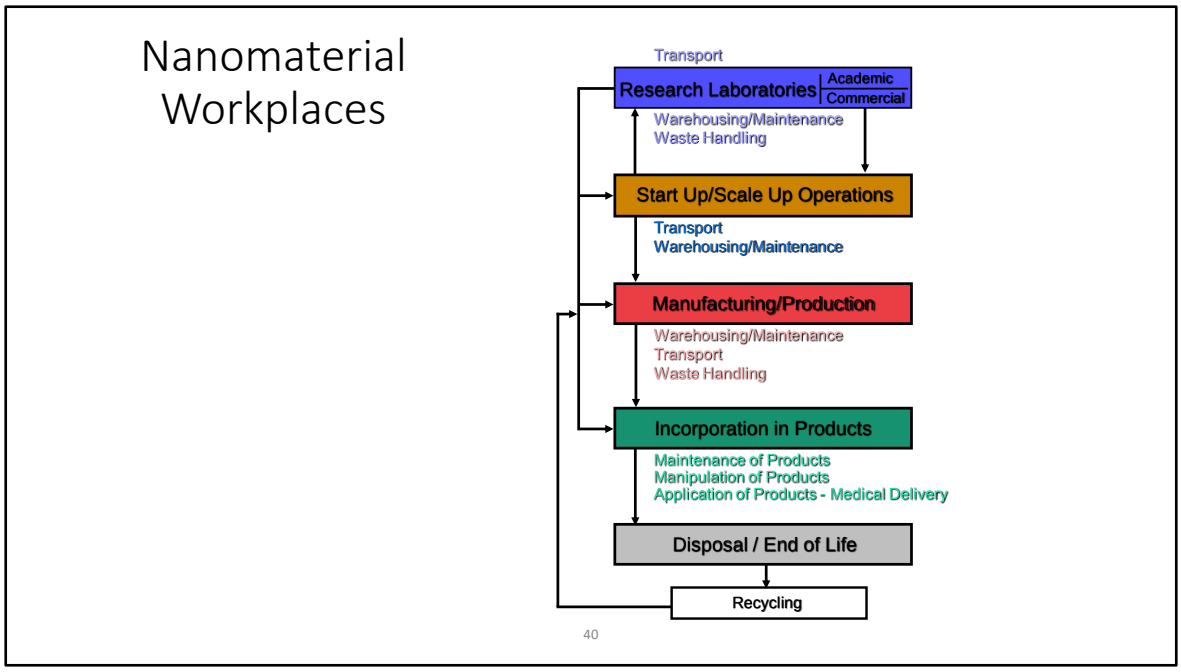
Factors that affect assessment of ENM health effects

- Immense universe of potentially unique ENMs and great diversity in toxic potential
- Assumed low extent of exposure due to global attempt to promote responsible development of the technology
- **Difficulty assembling study cohorts of similarly exposed workers**
- Lack of clarity on appropriate early indicators or biomarker of adverse effects

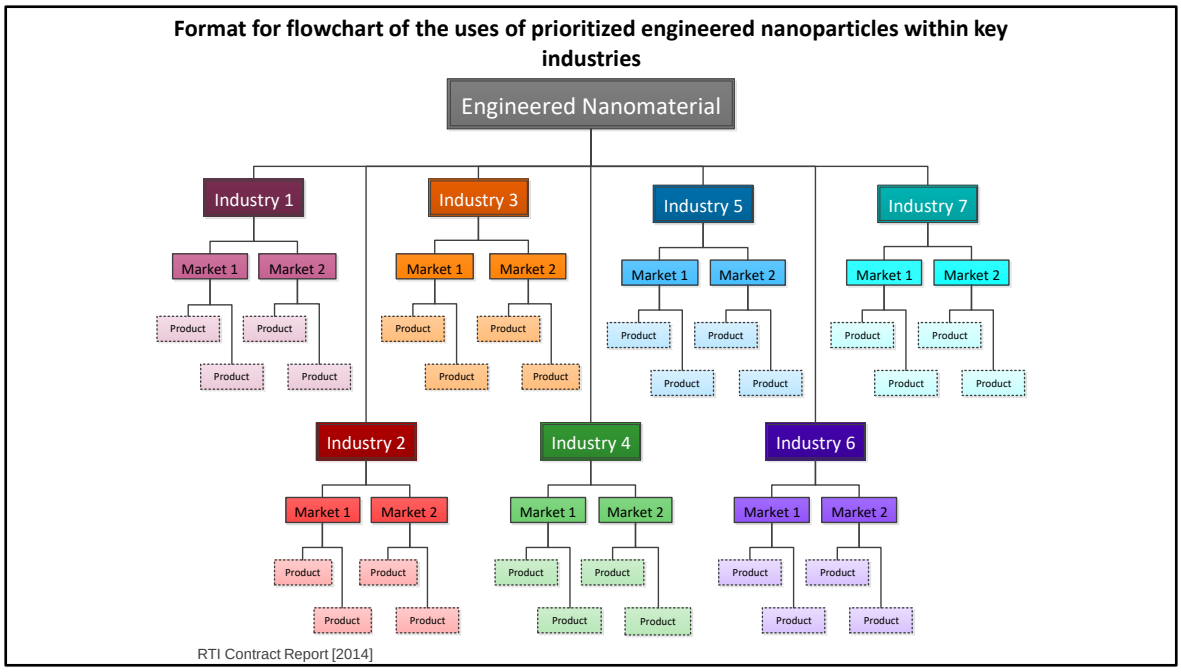
39

>> Paul Schulte: Another issue in figuring out the health effects is to try to find cohorts of similarly exposed workers.

A key in epidemiology is to compare groups of people who have the same hazardous exposure to people who don't or who have a lesser one. With so many different kinds of engineered nanoparticles, it's difficult to make that comparison.

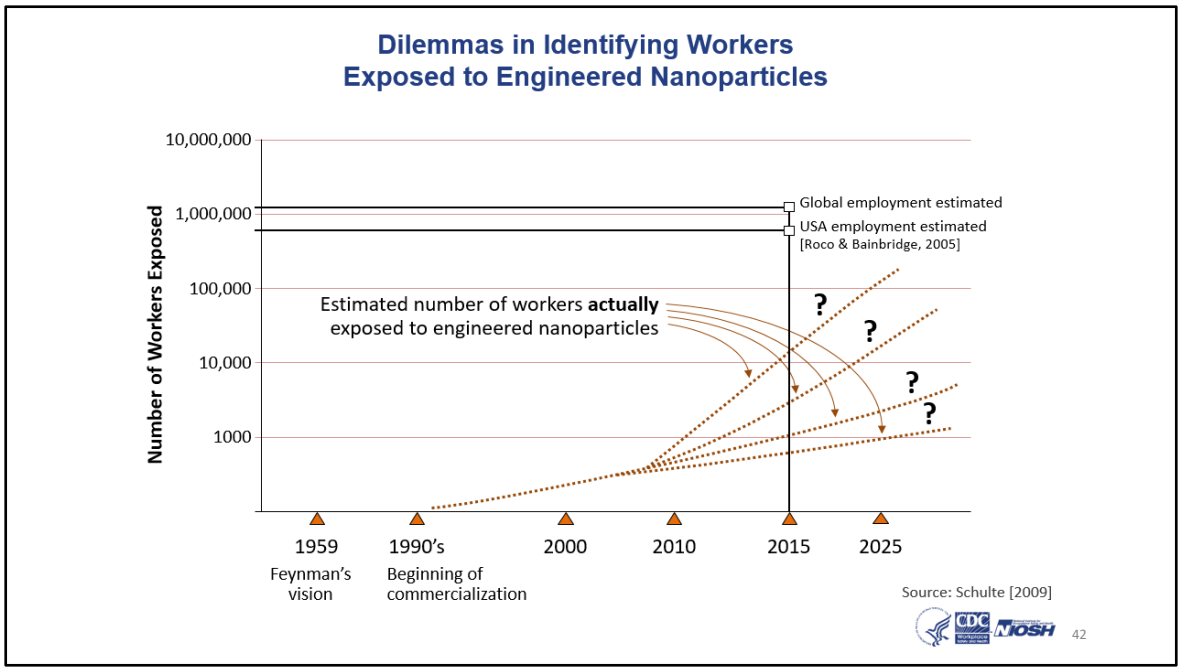


>> Paul Schulte: Indeed, you can look all through the life cycle of products, of nanomaterials: there are workers at every different step in the life cycle.



>> Paul Schulte: The problem is, they may not be exposed to the same material, so getting them into a large enough group to have statistical power is an issue, particularly with the technology that has vital business intelligence information that companies don't want to share.

Consequently, it's difficult to assemble study cohorts. And indeed, while we can conceptualize all the places where nanomaterials might be used, actually getting access to these places, finding similarly exposed people, and assembling the cohorts, are difficult.



>> Paul Schulte: Moreover, as I said, we're at about 20 years into the commercialization of engineered nanomaterials. That doesn't leave a long time for two things:

- One, for enough people to have exposure. Exposure didn't happen 100% right at the beginning, it gradually grew, as that picture of the products and commerce Joanna showed. And so did the number of workers.
- Two, in some cases for some diseases, particularly some chronic diseases, you need what's known as a *latency period*, an adequate amount of time between the initial exposure and the appearance of the adverse effect. For diseases like cancer, that can take 10 to 40 years, generally. For nonmalignant diseases, that can still take a goodly number of years. So we didn't have that.

Factors that affect assessment of ENM health effects

- Immense universe of potentially unique ENMs and great diversity in toxic potential
- Assumed low extent of exposure due to global attempt to promote responsible development of the technology
- Difficulty assembling study cohorts of similarly exposed workers
- **Lack of clarity on appropriate early indicators or biomarker of adverse effects**

43

>> Paul Schulte: Besides those reasons, there's the fact that we didn't know precisely what are the adverse effects of engineered nanomaterials.

Disease endpoints

- Acute
- Chronic
- Distinguish from effects of air pollution and other industrial exposures

44

>> Paul Schulte: We understood from air pollution epidemiology, which involves nanomaterials, that respiratory and cardiovascular effects could occur. But there were still a lot of questions about what to look for in epidemiologic studies and how to design them to capture acute effects, or chronic effects, or to distinguish the effects from air pollution in other exposures that are more common to people and could interfere with the interpretation of the finding.

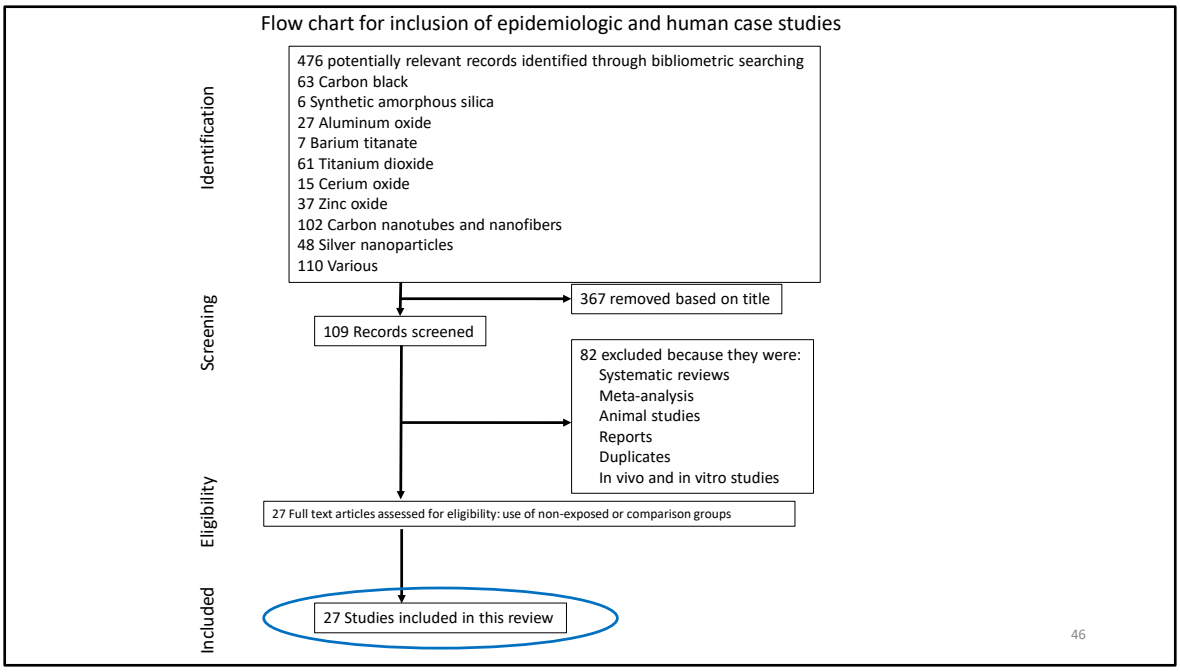
Nine most widely found engineered nanomaterials in commerce

Nanomaterial	Commercial Tonnage (Tons)[1]
Carbon black	9,600,000
Synthetic amorphous silica	1,500,000
Aluminum oxide	200,000
Barium titanate	15,000
Titanium dioxide	10,000
Cerium dioxide	10,000
Zinc oxide	8,000
Carbon nanotubes/nanofibers	100-3000
Silver nanoparticles	20

1. Based on WHO report (2017)

45

>> Paul Schulte: What we did in this study – again we're taking stock of what we know about the health effects on workers – we took the nine most widely used materials in commerce by tonnage. You can see them listed by tonnage, from largest to smallest, the top nine.

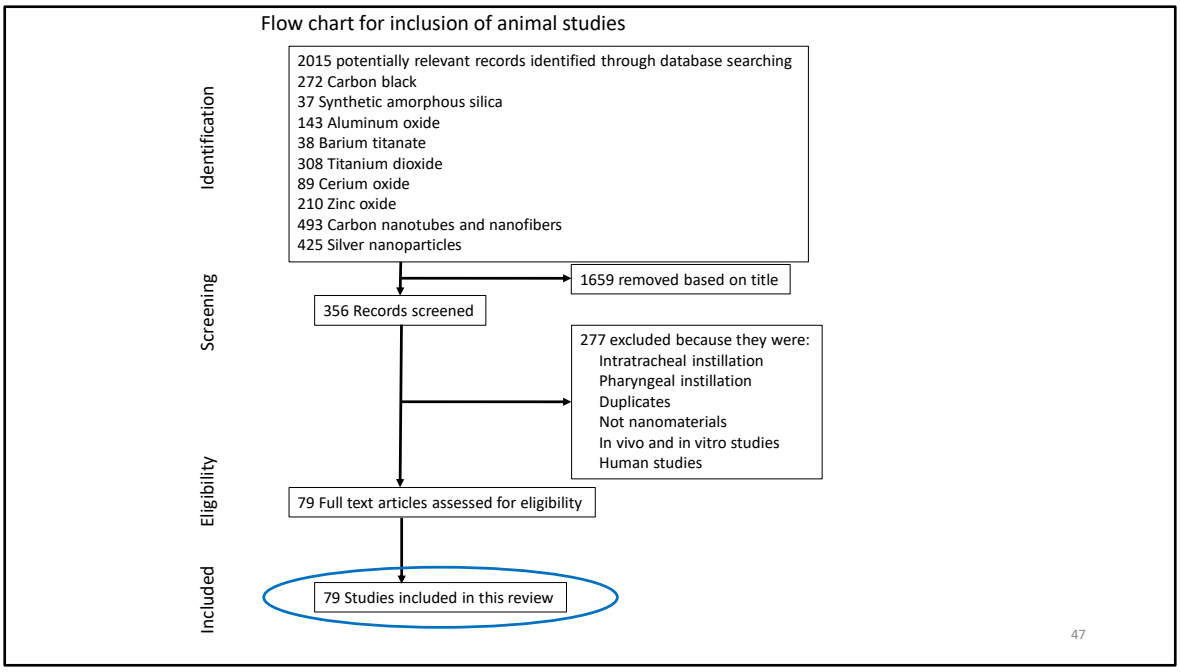


>> Paul Schulte: We then did a literature search looking for them, using a certain variety of key words, and their names, various forms of their names.

We went through the literature using, finally, as an exclusion criterion, that we identified a study that had the use of a non-exposed or a comparison group in it. If it didn't have that, we didn't consider it an adequate epidemiologic study.

Out of the literature, where we started with about 476 studies, we came out with 27 studies to include in this review.

Some of those 27 studies include the same populations studied for different end points or from a different angle, so there's not actually 27 discrete groups. But there are 27 studies that we looked at.



>> Paul Schulte: Also, just to supplement what we did and corroborate some of the findings, we did a similar search of the animal literature, looking just for inhalation studies, animal inhalation studies. Inhalation is the primary route of exposure of workers to dust, and we were concerned – we were looking for corroboration – of what we might see in the animal epidemiologic studies, and we came out with 79 studies here.

This is not going to be a report on these, but I'll bring them in occasionally where it's appropriate.

Carbon Black

- Generic name for family of materials
- Primary particle range 10-500 nm
- Aggregates 50-600 nm; agglomerates <2 μm
- Legacy ENM; manufactured for >80 yrs

48

>> Paul Schulte: Okay. To go through the nine groups, here's the first group: carbon black. You may say carbon black has been around a long time; indeed. it's been around for more than 80 years. You might call it a legacy engineered nanomaterial.

It's an engineered nanomaterial because there are many different kinds of carbon black. It's a generic name for a family of materials; they are produced based on different parameters of temperature and pressure and other characteristics to get the kind of functional properties for the individual product. In that broad sense, they are engineered nanomaterials.

They are not the high-tech ones that we're talking about generally when we talk about nanotechnology, but they do represent materials that have a primary particle range in the lower ends of the nano spectrum, in this case, from 10-500 nanometers. But they aggregate and agglomerate, they glom together, and that way influence their aerodynamics, inhalability, respirability, and so forth.

That's the first group, carbon black.

Carbon Black

- Strong epidemiologic evidence of association of nonmalignant respiratory morbidity/pulmonary function decrement, symptoms of chronic bronchitis, and production (Gardiner et al. 2001; VanTongeren et al. 2002; Harber et al. 2003, Neghah et al. 2011)
- Alterations in carbon black nanomaterial workers of respiratory function parameters and inflammatory cytokines (Zhang et al. 2014; Dai et al. 2016)
- Animal studies showed pulmonary inflammation (Vesterdahl et al. 2010; Niwa 2008; Zhang et al. 2014; Li et al. 2014)

49

>> Paul Schulte: The literature on it, you'll see the literature on all of these materials, is diverse and strong or weak in different areas.

In this case there's strong epidemiologic evidence of an association with nonmalignant respiratory morbidity, decremental pulmonary function, chronic bronchitis, and so forth, with production. There's a fairly rich body of literature looking at that.

There are also some studies of respiratory function in more contemporary engineered nanomaterials made specifically to be of a common nanometer size, and there, those studies have shown decrement in respiratory function and appearance of inflammatory cytokines, so indications of pulmonary inflammation. Similarly, pulmonary inflammation was corroborated in a variety of animal studies.

Carbon Black

- Lung Cancer evidence inconsistent (IARC 2010)
  - Review of a industry-based case/control or cohort studies and community studies were assessed
  - 7 of these 13 were considered informative for lung cancer (3 in production workers)
  - Generally cohorts small; confounding by cigarette smoking could not be excluded
  - Animal studies support that carbon black can cause lung cancer in animals (IARC 2010)
- IARC (2010) classifies carbon black as a possible human carcinogen

50

>> Paul Schulte: Now lung cancer is a different picture. There have been a goodly number of studies of lung cancer. IARC (International Agency for Research on Cancer) looked at the issue in 2010, identified 13 studies: seven of them appeared to be informative for lung cancer, but they were generally small cohorts and they didn't control well for cigarette smoking, so there was potential confounding for that, that could be excluded. So basically, the epidemiologic evidence was inconclusive.

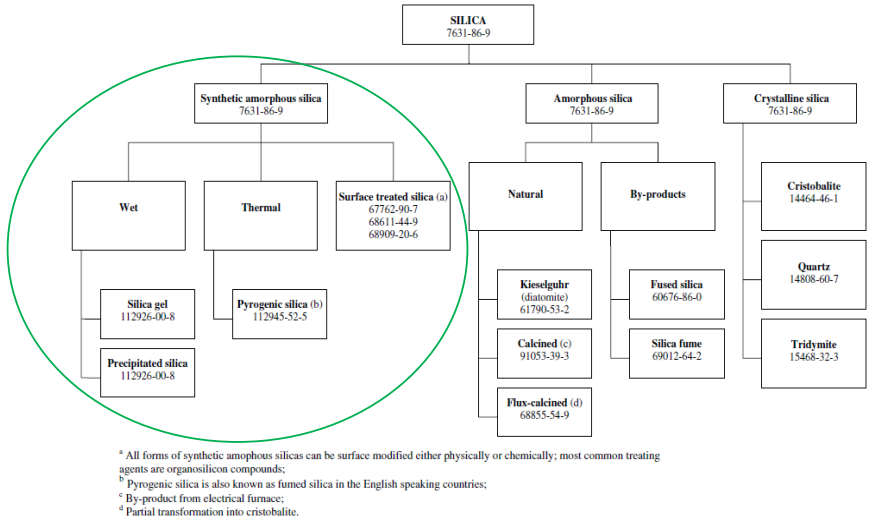
However, IARC looked at the animal studies and showed that they did support that carbon black can cause lung cancer; in 2010 it classified that carbon black as a possible human carcinogen based on animal studies.

Synthetic Amorphous Silica (SAS)

- Been in commerce for more than 60 years
- Intentionally manufactured; no measureable levels of crystalline silica
- Primary particles less than 100 nm

51

>> Paul Schulte: The next big category is synthetic amorphous silica. The silicates are a wide family of materials. This, too, is essentially a legacy nanomaterial. The variety of products that are made are produced by different parameters in the production process. This material is distinguished from crystalline silica; it is intentionally manufactured with no measurable level of crystalline silica. Generally the particles are less than 100 nanometers.



[a] All forms of synthetic amophous silicas can be surface modified either physically or chemically; most common treating agents are organosilicon compounds;
[b] Pyrogenic silica is also known as fumed silica in the English speaking countries;
[c] By-product from electrical furnace;
[d] Partial transformation into cristobalite.

Fig. 1. Different polymorphs of silica with CAS numbers.

(Arts et al. 2007)

52

>> Paul Schulte: This is a diagram of the various silica polymorphs; we're looking at this group, synthetic amorphous silicates, particularly the pyrogenic silicas, fumed silica, which is used in a wide variety of industrial and commercial products.

Synthetic Amorphous Silica (SAS)

- Primary particles <100 nm; aggregates and agglomerates size (μm)
- Not comprehensively studied
- Epidemiologic record back to 1932 did not show fibrosis; did not exclude risk of COPD, emphysema or cancer (Merget et al. 2002)

53

>> Paul Schulte: Now, with the synthetic amorphous silica, the primary particles are less than 100 nanometers, but you still see a fairly large amount of aggregation and agglomeration. Again there are issues of, well, the primary particle is nano, but what people breathe in might be in the micro range.

These materials haven't been comprehensively studied. There has been some epidemiologic work that went back to 1932 that didn't show anything in terms of pulmonary fibrosis, which you might expect with silicas. But the studies weren't designed to look for chronic obstructive pulmonary disease, emphysema, or cancer, so the epidemiologic record is not too strong.

But at least it was clear in the area of fibrosis.

Synthetic Amorphous Silica (SAS)

- Subset of workers in 14 factories in Taiwan, N = 31
  - Silicon dioxide ENMs (12-200 nm)
  - Urinary 8-OHdG and 8-isoprostane significantly increased compared with controls
  - Global DNA methylation significantly decreased

(Liou et al. 2017)

- 8-OHdG-good indicator of repair of oxidative damage to DNA

54

>> Paul Schulte: Now, in more contemporary times, in a subset of 14 factories in Taiwan that produced a variety of different engineered nanomaterials, a subset of those factories and workers in them who had, almost exclusively, exposure to synthetic amorphous silica, was studied. Essentially, what we see here are markers indicative of oxidative stress. Oxidative stress is certainly the imbalance between free radicals and antioxidants, and when you have more of the free radicals, you can get to a situation that can lead to a myriad of different kinds of health effects.

So you'll see in a lot of these studies that they are not looking for a health effect *per se*, they are looking for a marker of some sort of damage, generally oxidative damage. That was seen with this group.

Synthetic Amorphous Silica

- Animal inhalation studies
  - Partially reversible inflammation
  - Granuloma formation
  - No progressive fibrosis (Arts et al. 2009)
- SAS nanoparticles penetrated from nose to brain (Katsnelson et al. 2015)
- Fumed silica has been shown to generate cytotoxicity and pro-inflammatory effects

55

>> Paul Schulte: However, in some animal studies there was no indication of really extensive inflammation; it was partially reversible, no fibrosis, a little bit of granuloma formation. So there's not big animal literature supporting health effects from synthetic amorphous silicate.

There is an intriguing finding that particles penetrated from the nose to the brain. And indeed, this is a mechanism for a lot of different kinds of nanomaterials; to see this happening always gives us pause, albeit we're not sure of the pathologic significance of it.

And then, for the fumed silicates, the pyrogenic silica I showed you, it has been shown to generate cytotoxicity and pro-inflammatory effect in some animal studies. So there is some concern, but it's not a strong case at this point.

Case Study

- 7 female workers (18-47 yrs) in a print plant
- Silica nanoparticles (2-20 nm) in pleural effusions
- Pulmonary fibrosis and inflammation
- Pleural granuloma

(Song et al. 2011)

56

>> Paul Schulte: There is one case study that is nagging in the literature for its ability to raise concern, but not very conclusive. Seven workers in a print factory were all hospitalized. Silica nanoparticles were found in pleural effusion. They had pulmonary fibrosis and inflammation and pleural granulomas – they were pretty sick. But this study was a case study, there wasn't good exposure assessment, and the linkage to the nanoparticles is questionable.

Albeit it needs to be always mentioned, I think, because it could be a signal or it could be just a false alarm.

Aluminum Oxide

- No epidemiological studies of nano-aluminum oxide
- Occupational studies of worker exposed to aluminum dusts, including aluminum oxide (may have included nano-aluminum oxide)
  - Pulmonary fibrosis
  - Asthma
  - Chronic obstruction lung disease
  - Lung cancer

  (Björ et al. 2005, Jederlinc et al. 1990; Kraus 2006, Mazzoli-Roiha et al. 2010)
- Ultrafine particles have been found in aluminum smelters and pot rooms

  (Thomassen et al. 2005)

57

>> Paul Schulte: The next category is aluminum oxide. And there are no epidemiological studies of nano aluminum oxide. This will be a mantra you'll hear through a lot of the rest of this summary.

Occupational studies have been performed on workers exposed to aluminum -- aluminum dust, aluminum oxide -- and they may have included nano aluminum oxide, but it wasn't necessarily focused on. So the best you can say is there is association of aluminum and aluminum oxide with pulmonary fibrosis and asthma, chronic obstructive lung disease, and in some studies, lung cancer.

Also, in aluminum smelters and pot rooms, ultrafine particles have been found, some of which were nanoscale, but not generally a lot of them.

Aluminum Oxide

- Inhalation studies of rats exposed to 10 nm aluminum oxide
  - 0, 50, 100, 160 mg/m^3
  - 6 hrs/day for 5 days
- Showed dose-dependent:
  - Pulmonary inflammation
  - Cytotoxicity (on history)

(Rajsekhar et al. 2014)

58

>> Paul Schulte: Animal studies looking at aluminum oxide, nanomaterials: aluminum oxide, 10 nanometers, showed pulmonary inflation and cytotoxicity in a dose-dependent fashion.

And so for aluminum oxide, we need to pay attention to it when we can find the right population.

Barium Titanate

- Member of large family of ABO_3 materials known as perovskites
- No documentation of occupational exposure or animal inhalation studies
- Curious that such a relatively high use (4th in volume) material has not been studied

59

>> Paul Schulte: The next -- the fourth most widely used, one of the ABO_3 group of materials -- that's where AB can be any of different kinds of ion, and with oxygen. These materials are known as perovskites; they are used widely in electronic products. It's funny, for being the fourth-highest volume material in commerce, there are practically no animal studies, really no animal inhalation studies that I could find, and no epidemiologic studies. This is an area that merits extensive further study.

Titanium Dioxide

- In use since the 1920's
- Particle size plays a role in application
  - Pigments 200-350 nm
  - Electronics, photocatalytics: <100 nm

60

>> Paul Schulte: We come to titanium dioxide. Again, it has a certain legacy role going back to the '20s. Its particle size relates to how it can be used. (We're running out of time so I'm going to speed along here.)

Titanium Dioxide

- Epidemiologic studies of production workers showed little evidence of malignant or nonmalignant effects (particle size not well documented)
- IARC (2010) concluded epidemiologic data for cancer was inadequate
  - One study (Boffetta et al. 2004) found excess lung-cancer SMR 1.23 (1.10-1.38) but no exposure-response relationship; particle size not assessed

61

>> Paul Schulte: Epidemiologic studies of production workers shows little evidence of malignant or non-malignant effect. However, IARC concluded the epidemiologic data was inadequate.

There was one study that found an excess of lung cancer but no exposure response relationship, and particle size was not addressed, so we don't know if they were talking about nano titanium dioxide or larger.

Titanium Dioxide

- Epidemiological studies of nano-TiO_2 report alterations of oxidative stress biomarkers in exhaled breath

- Lipid oxidative markers: malondialdehyde, 4-hydroxyl-trans-hexenal, 4-hydroxyl-trans-nonenal, 8-isoProstaglandin F2a and aldehydes C6-C12 (Pelclova et al. 2017a, 2017b);

- High levels of urinary 8-OHdG and 8-isoprostane in exposed vs control workers (Liou et al. 2017)

62

>> Paul Schulte: Studies of nano titanium dioxide in workers have shown essentially a wide variety of oxidative stress biomarkers, so indeed again, this seems like a source of oxidative stress.

And I'm not going to belabor that. I'll just keep going along here.

Titanium Dioxide

- A significant dose dependent increase in the pulmonary surfactant protein D serum levels, as a biomarker of lung damage was detected in workers employed in a packaging workshop of a nano-TiO_2 manufacturing plant in eastern China (Zhao et al. 2018)
- Alterations in cardiovascular disease markers, i.e. VCAM-1, ICAM-1, LDL, and TC were associated with occupational ENM exposure (Zhao et al. 2018)
- Reduced pulmonary function (FVC; FEI 25-75%; FEVI) in workers (Zhao et al. 2018)

63

>> Paul Schulte: (No discussion of this slide.)

Titanium Dioxide

- Chronic inhalation studies of rats
  - Primary particles size 15-40 nm
  - Bronchoalveolar hyperplasia
  - Squamous cell carcinoma (lung)
  - Adenocarcinoma (lung)

  (Heinrich et al. 1995; Lee et al. 1985)
- Lung overload lead to secondary genotoxic mechanism of carcinogenicity
- IARC (2010) considered there was sufficient animal evidence that titanium dioxide is "possibly carcinogenic to humans"

64

>> Paul Schulte: Some chronic inhalation studies in rats, though, were able to show squamous cell lung cancers. IARC looked at this and considered the animal evidence was sufficient that titanium dioxide should be classified as possibly carcinogenic to humans.

The mechanism is of secondary genotoxicity related to lung overload, and there's an argument in the literature about the significance of that.

Cerium Oxide

- Cerium oxide nanoparticles increasingly being used in broad array of applications
- Epidemiological studies of workers are lacking
- Animal inhalation studies
  - Pulmonary inflammation
  - Expression of CINC-1, CINC-2, HO-1 in BALF
  - Pulmonary fibrosis
  - Discrete granulomas
  - Tubular degeneration leading to kidney necrosis

(Morimoto et al. 2015, Demokritu et al. 2017, Alapati et al. 2014, Ma et al. 2015)

65

>> Paul Schulte: Cerium oxide is the next most widely used material. It is used in a broad variety of applications; the number is growing. Unfortunately, there are no epidemiological studies of it.

Animal studies, again, show a variety of health effects, some related to pulmonary inflammation, fibrosis, and some kidney necrosis.

Zinc Oxide

- No epidemiological studies of exposure to zinc oxide ENM
- Experimental study of Zn-O fume (60 nm MMAD) (2.5 mg/m^3 and 5mg/m^3 for 2 hours) in 13 healthy non-smoking volunteers
  - Metal fume fever at 5mg/m^3, no change in pulmonary function
  - Increased specific airway resistance
  - Elevated plasma IL-6, cough, fatigue

(Gordon et al. 1992)

66

>> Paul Schulte: The next category are zinc oxide studies. Zinc has been around for a long time. There are no epidemiological studies of exposure to zinc oxide.

Experimental studies of volunteers compared healthy to exposed workers and showed metal fume fever, a widely known pulmonary effect, but no decrement in pulmonary function.

Zinc Oxide

Animal studies

- Acute inhalation (6 hrs) to 35 nm at 2.4, 3.7, and 12.1 mg/m^3
  - Increase neutrophil counts at 2.4 mg/m^3
  - Role for zinc ions (Ho et al. 2011)
- 4 wk study of rat inhalation exposure to 35nm
  - No persistent inflammation

(Morimoto et al. 2016)

- 13 wk inhalation of mice to 15-26 nm at 3.5 mg/m^3

(Adamcakova-Dodd et al. 2014)

  - Minimal pulmonary inflammation, cytotoxicity or lung histopathological changes

67

>> Paul Schulte: In terms of zinc oxide, animal studies have shown some pulmonary effects but minimal, not considered too problematic in that regard.

Carbon nanotubes/nanofibers

- Relatively recently discovered/invented (since 1990's but with historical antecedents)
- Extraordinary mechanical, electronic, transportation, electrical and optical properties
- Many different types (tens of thousands)

68

>> Paul Schulte: Then we come to a whole raft of studies on carbon nanotubes. I'm not going through each of these because there are about 20 of them. But they start out from very primitive…

First of all, there are many kinds of carbon nanotubes, and comparing the right ones is difficult.

Carbon nanotube/nanofibers

Epidemiological studies

- Cross-sectional epidemiological studies
  - Most use biomarkers as dependent variables
  - Exposure assessment: weak to strong
- Comparison of 9 MWCNT workers and 4 Office Workers
  - Manufacturing workers had significantly higher levels of aldehydes (MDA, 4- HHE, n-hexanal)
  - Study showed no adverse health effects
  - Some markers of oxidative stress

(Lee et al. 2015)

69

>> Paul Schulte: But when you start to compare, in primitive studies, nine carbon nanotube workers and four office workers, you start to see indications of oxidative stress.

And then when you get into more exquisite studies where you have gender- and age-matched controls, you still see a variety of effects of immune and pulmonary markers and oxidative stress.

Carbon nanotubes/nanofibers

Epidemiological studies

- 10 MWCNT exposed and 12 non-exposed controls
- Exposure associated with significant increases in IL-13, IL-6, TNF-, KL-6

(Futkhutdinova et al. 2016)

- 8 MWCNT exposed and 7 non-exposed
- Aberrant changes in miRNA and ncRNH expression profiles in exposed workers
- Number of dysregulated mRNA and miRNA associated with pulmonary inflammation and fibrosis

(Shvedova 2016)

70

>> Paul Schulte: I'm going to skip through some of these.

And so what we're seeing is concern about carbon nanotubes in terms of oxidative stress, pulmonary markers. And then this intriguing study by Shvedova and colleagues of a variety of micro and messenger and non-coding RNA expression profiles that indicate consistent patterns of pulmonary inflammation and fibrosis. There needs to be concern there.

Carbon nanotubes/nanofibers

Epidemiological studies

- Cross-sectional study of 100 workers in 12 U.S. plants
  - Presence of CNT in sputum; association with sputum and blood biomarkers
  - CNT exposure suggest systemic inflammation and potential for cardiovascular dysfunction

(Beard et al. 2018)

Inhalable CNT and CNF positive association with the development of respiratory allergies (Schubauer-Berigan et al. 2018)

71

>> Paul Schulte: (No discussion of this slide.)

Carbon nanotubes/nanofibers

Epidemiological studies

- 21 exposed to MWCNT and 21 age/gender-matched controls
- Early effects on lung health and immune system
- Significant upward trends immune and pulmonary markers
  - C-C motif ligand 20
  - Basic FGF
  - Soluble IL1-receptor
  - FENO

(Vlaanderen et al. 2017)

72

>> Paul Schulte: (No discussion of this slide.)

Carbon nanotubes/nanofibers

Epidemiological studies

- Cross-sectional study (MWCNT)
- 22 exposed and 42 matched unexposed
- 13 exposed and 6 unexposed (after 5 months)
- Upward trend: endothelial damage maker; intercellular adhesion molecule 1 (ICAM-1)
- Trends positively associated with exposures

(Kuijpers et al. 2018)

73

>> Paul Schulte: (No discussion of this slide.)

Carbon nanotube/nanofibers

Animal studies

- Nonmalignant respiratory effects
- Pulmonary Fibrosis (Dong and Ma 2018)
- NIOSH (2013) reviewed 54 animal studies
  - Inflammation (44/54)
  - Granulomas (27/54)
  - Pulmonary fibrosis (25/54)
- Cardiovascular Effects
  - Cross talk between pulmonary and systemic circulation
  - May trigger or exacerbate cardiovascular dysfunction and disease (eg atherosclerosis) (Erdeley et al. 2008)
  - IT studies: sustained cardiovascular inflammation (Chen et al. 2015)
- Malignant effects
  - Inadequate or limited evidence for most types of CNT (Kuempel et al. 2017; IARC 2014)
  - Possible carcinogenicity of one type MWCNT-7 (IARC 2014; Kuempel et al. 2017)

74

>> Paul Schulte: Certainly, NIOSH has identified carbon nanotubes as being highly related to pulmonary fibrosis in animals.

Silver nanoparticles

- Silver nanoparticles used for over 100 years
- Silver nanoparticles most common in consumer products inventory
- Demand for different nanostructures such as spheres and wire
- Have different physicochemical properties

75

>> Paul Schulte: The last category is silver nanoparticles. They've been around for a long time.

Silver nanoparticles

- No adverse health effects in cross-sectional study of workers exposed to silver (20-30 nm)

  (Lee et al. 2011, 2012)

- 13 week rat inhalation studies of silver (18 nm) at doses of 0, 49, 117 or 514 mg/m^3
  - Lung function deficits
  - Decreased: tidal volume, minute volume, peak inspiration flow
  - Macrophage accumulation

  (Sung et al. 2008)

  - Follow-up 12 weeks after exposure: persistence of lung dysfunction
  - Exposure-related decrease in lung function

  (Song et al. 2013)

76

>> Paul Schulte: (No discussion of this slide.)

Silver nanoparticles

Animal studies

- 13-week inhalation study-Sprague-Dawley rats
  - 2-65 nm, median 16nm
  - 0, 49, 133, 515 ųg/m^3
  - Resulted in bile duct hyperplasia

(Sung et al. 2009)

77

>> Paul Schulte: NIOSH is about to put out a new occupational exposure limit based on these inhalation studies that show pulmonary effects and bile duct hyperplasia effects in animals. We'll have a new nano REL (recommended exposure limit) for silver.

Summary of Epidemiological and Animal Data for ENMs by Commercial Volume

Nanomaterial[a]	Commercial Tonnage (Tons)	Epidemiologic findings pathologic effects in workers	Potential biomarkers of adverse effects in epidemiological studies of workers	Adverse effects in animals
Carbon black	9,600,000	++++ Nonmalignant respiratory disease	+ + Pulmonary function; +++Pulmonary inflammation	+ + +Lung cancer; + + ++ Pulmonary inflammation
Synthetic amorphous silica	1,500,000	n.a.	+++ Oxidative stress ++ DNA methylation	++ NMRD +++ Fumed silica
Aluminum oxide	200,000	n.a.	n.a	+++ Pulmonary inflammation
Barium titanate	15,000	n.a.	n.a.	n.a
Titanium dioxide	10,000	+ Lung cancer + NMRD	+++ Inflammatory and oxidative stress ++ Pulmonary disease +++ Cardiovascular disease	+ + + + ROS and pulmonary inflammation ++ Genotoxicity +++ Lung cancer
Cerium dioxide	10,000	n.a.	n.a.	+++ Pulmonary inflammation; fibrosis
Zinc oxide	8,000	+++ Metal fume fever	n.a.-	+ + + Acute inflammatory change
Carbon nanotubes/nanofibers	100-3000	n.a.	+ + + Pulmonary, Immunological, Cardiovascular ++ Gene-specific DNA methylation	+ + + + Pulmonary inflammation + + + + Fibrosis + + + Cardiovascular +++/++++ Cancer (MW-CNTs7)
Silver	20	n.a.	n.a.	+ + + Pulmonary inflammation + + + Liver effects including bile duct hyperplasia

n.a. = not available
a: list in table by tonnage
+ to ++++ represents a range of strength of evidence

78

>> Paul Schulte: In conclusion, what we have here is a situation where most of the epidemiological studies are generally negative, except for nonmalignant respiratory disease in carbon black, a little bit of nonmalignant disease with titanium dioxide and one study on lung cancer, and metal fume fever in zinc oxide.

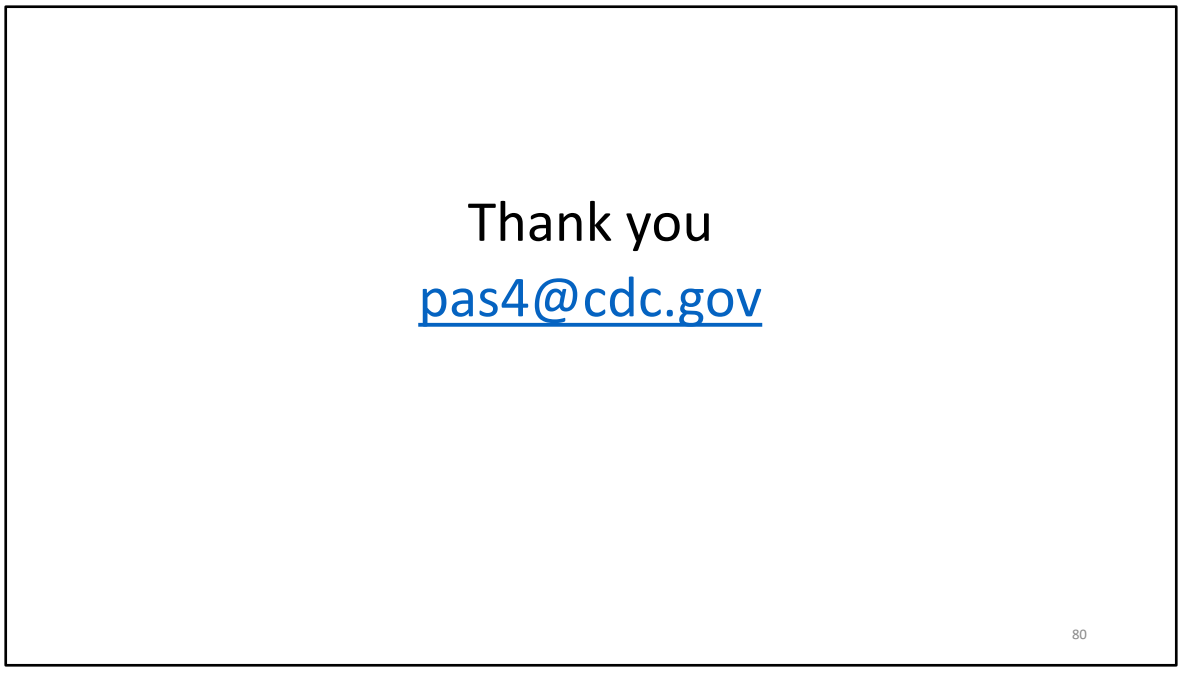
Conclusions

- ENMs need to be considered by type with regard to health effects
- Generally there are few studies of health effects of contemporary ENMs; some for legacy ENMs but findings are suggestive
- Need to take next step and continue to further study worker populations
- Need to conduct animal studies to support worker findings
- Need to assess biomarkers across studies as well as within them
- Precautionary risk management approaches are still warranted

79

>> Paul Schulte: Generally we don't see any effects in workers in terms of frank effect. But there is a growing body of information on biologic markers of inflammation and oxidative stress and cardiovascular disease.

That would be where we would want to go from here.



>> Paul Schulte: I think I'll stop so we can squeeze in a few questions.

Thank you very much.

Q/A

What is your view based on evidence about consumer exposure to nano-enabled products? You showed quite a few. As a consumer should I be worried, or should I be waiting for additional studies? What's your overall position?

81

>> John Howard: Thank you, Paul.

The first question I wanted to ask: Joanna, what is your comprehensive view based on the evidence to date about consumer exposure to nano-enabled products? You showed quite a few nano-enabled products. As a consumer should I be worried, or should I be waiting for additional studies? What's your overall position?

>> Joanna Matheson: Well, it's not my position, but at least from the work that's been done so far, most of the studies have shown that for consumers, the exposures are low. But one of the things that we do want to do is – these were all exposure hazard assessments – is to assess the robustness of the data and to start doing some risk assessments on it.

I expect that probably we'll start off with some of the silver studies.

You can see the majority of the projects have been on the three major nanomaterials, just because those are the most common consumer products, the TiO_2, the nano silver, and the carbon nanotubes. So we certainly plan on carrying these to the next stage.

Q/A

Are there any occupational exposure limits that have been set for workers for these nano products?

82

>> Paul Schulte: Thank you, Joanna.

Paul, are there any occupational exposure limits that have been set for workers for these nano products?

>> Paul Schulte: There are a few. Clearly, NIOSH has occupational exposure limits for titanium dioxide and carbon nanotubes. But there are so many different kinds of these materials that it's not clear to what extent all the different kinds are covered by one limit.

Europeans have some categorical exposure limits in place, and a few others have been set. NIOSH is coming out with one on silver. There are very few that have been promulgated as rules by official government agencies, though.

Q/A

Is Underwriters Laboratories involved in any of the 3D printing studies?

83

>> John Howard: Thank you, Paul.

Joanna or Paul might be able to answer the question as to whether the Underwriters Laboratory is involved in any of the 3D printing studies.

>> Paul Schulte: I have no knowledge of that. Maybe Joanna does.

>> Joanna Matheson: No. At least for interagency agreements directly with us, they are not.

I can't be sure whether some of their partner researchers may be. And certainly the agency as part of the whole additive manufacturing work going on, some of the work going on at ASTM, there is interaction there. I'm not part of that, but yes.

Q/A

Is there agreement on the size range of what we're all calling a nanoparticle, a nanomaterial?

84

>> John Howard: Thank you.

One of the questions that one of the listeners is asking is, “Is there agreement on the size range of what we're all calling a nanoparticle, a nanomaterial?”

>> Paul Schulte: Well, all-size particles, generally, that can be breathed in have health effects. For commercial scientific purposes, an arbitrary level of one to 100 nanometers is the agreed range of concern. But that's just an arbitrary upper limit; that doesn't mean a 150 nanometer particle can't have health effects. But for some sort of standardization of discussion and practice, one to 100 nanometers is the range.

Q/A

Would a nanomaterial, nanoparticle be listed on a safety data sheet? If I was a worker looking at a nano process in my workplace, would I find it there?

85

>> John Howard: Paul, would a nanomaterial, nanoparticle, be listed on a safety data sheet? Would we be able to find it if I was a worker looking at a safety data sheet? Or I was looking at a nano process in my workplace, would I find it there?

>> Paul Schulte: Possibly, but not generally.

We've done a couple of studies looking at safety data sheets. Some did not have any information about the nanomaterial component, when we knew it was there. Some had inappropriate information.

So safety data sheets need work. We hope that the papers we published have spurred people to write better ones.

Closing

Final remarks

86

>> John Howard: Well, thank you, Paul.

I want to thank our listeners. We're a little over time. We apologize for that. But a lot of great information was shared from Joanna and Paul. And we thank everybody for tuning in to this webinar.

Again, if you're interested in our series of webinars, please follow us on Twitter and @NNInanonews, and check nano.gov for more information on our upcoming webinars.

We thank you for your interest. Thank you, Dr. Matheson, Dr. Schulte, for excellent presentations. We look forward to our next presentation and seeing you all back.

So have a great rest of the day and thank you.