

Epidemiological Study of U.S. Carbon Nanotube Workers

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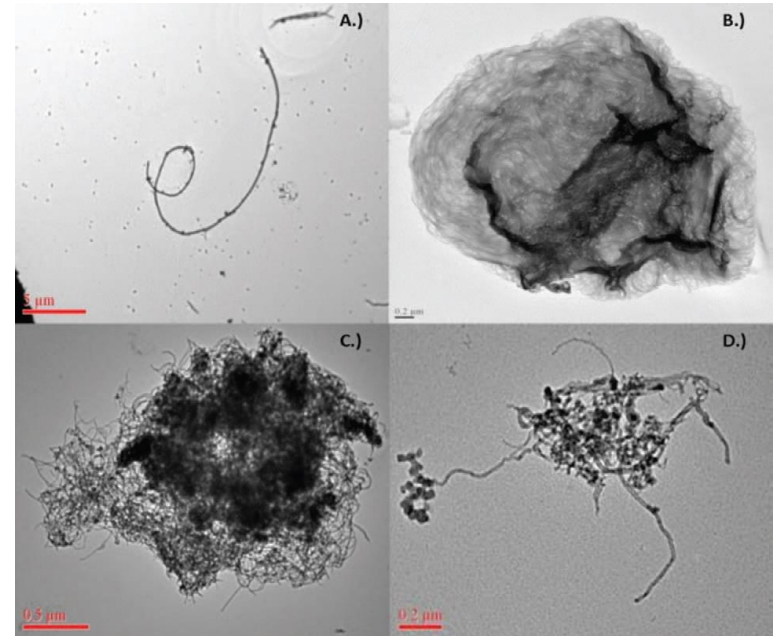
QEEN II: 2nd Quantifying Exposure to Engineered
Nanomaterials from Manufactured Products Workshop
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Study Objective

- Estimate associations between occupational carbon nanotube and nanofiber (CNT/F) exposure and early human health effects
- Study conducted by the National Institute for Occupational Safety and Health

Study Design

- Industrywide cross-sectional study
- 12 sites across the U.S.
 - Primary producers
 - Secondary users
 - Hybrid
- 108 CNT/F workers
 - 75% of recruited workers



From Dahm et al. (2015)

Exposure Assessment

- Personal breathing zone, filter-based air sampling
 - Background-corrected elemental carbon (EC) concentrations (2 variables)
 - CNT/F structure count concentrations (6 variables)



Exposure Assessment

- Direct-reading instruments
 - Fine and ultrafine particulate matter mass and count concentrations (3 variables)
- Other (4 variables)



Outcome Assessment

- 36 sputum biomarkers
- 37 blood biomarkers
- Chest symptoms and respiratory allergies since start of CNT/F work



Outcome Assessment

- Lung function
- Resting blood pressure (RBP)
- Resting heart rate (RHR)
- Complete blood count (CBC) components



Sputum Biomarker Factor Loadings

78% of
variance
explained

Colored
loadings
have
largest
magnitudes
for each
biomarker

Biomarker	Factor		
	1	2	3
<i>Cancer/Fibrosis</i>			
MUC-1/KL-6	0.16	0.84	0.08
MMP-2	0.77	0.44	0.15
MMP-7	0.09	0.88	0.16
TIMP-1	0.65	0.54	0.25
<i>Inflammation</i>			
α-2-M	0.93	0.07	0.07
Apo-AI	0.93	0.18	0.16
Apo-AII	0.91	0.24	0.02
IL-1 β	0.66	0.28	0.55
IL-6R-β	0.43	0.65	0.27
IL-8	0.59	0.66	0.31
IL-18	0.07	0.19	0.88
<i>Oxidative Stress</i>			
8-OHdG	0.45	0.38	-0.36
MPO	0.48	0.31	0.69
<i>Cardiovascular/Coagulation</i>			
Fibrinogen	0.71	0.23	0.36
PAI-1	0.58	0.53	0.27
VCAM-1	0.87	0.28	0.19

CNT/F and Sputum Biomarker Factors

Key

	Positive association p-value < 0.05
	p-value ≥ 0.05
	Inverse association p-value < 0.05

Variable	Factor		
	1	2	3
Inhalable EC			
Respirable EC			
Total CNT/F			
Single CNT/F			
CNT/F <1 μm			
CNT/F <2 μm			
CNT/F <5 μm			
CNT/F <10 μm			
CPC			
ELPI			
PM _{2.5}			
Sputum CNT/F			
Any CNT/F			
CNT/F duration			

CNT/F and Sputum Biomarkers

Variable	Fibrosis						
	KL-6	MMP-1	MMP-2	MMP-7	MMP-9	SPP-1	TIMP-1
Inhalable EC							
Respirable EC							
Total CNT/F							
Single CNT/F							
CNT/F <1 μm							
CNT/F <2 μm							
CNT/F <5 μm							
CNT/F <10 μm							
CPC							
ELPI							
PM _{2.5}							
Sputum CNT/F							
Any CNT/F							
CNT/F duration							

CNT/F and Sputum Biomarkers

Variable	Inflammation														
	α -2-M	Apo-AI	Apo-AII	CRP	Eotaxin-1	IL-1 β	IL-2	IL-4	IL-5	IL-6	IL-6R- β	IL-8	IL-10	IL-18	TNF- α
Inhalable EC											Red				
Respirable EC															
Total CNT/F														Blue	
Single CNT/F															
CNT/F <1 μ m															
CNT/F <2 μ m												Blue		Blue	
CNT/F <5 μ m														Blue	
CNT/F <10 μ m														Blue	
CPC															
ELPI											Red				
PM _{2.5}															
Sputum CNT/F															
Any CNT/F	Blue														Blue
CNT/F duration															Red

CNT/F and Sputum Biomarkers

Variable	Oxidative Stress			
	8-OHdG	GPx	MPO	SOD
Inhalable EC	Red	Yellow	Yellow	Red
Respirable EC	Yellow	Yellow	Yellow	Red
Total CNT/F	Yellow	Blue	Yellow	Red
Single CNT/F	Yellow	Yellow	Yellow	Red
CNT/F <1 μm	Yellow	Yellow	Blue	Red
CNT/F <2 μm	Yellow	Yellow	Blue	Red
CNT/F <5 μm	Yellow	Blue	Blue	Red
CNT/F <10 μm	Yellow	Blue	Blue	Red
CPC	Yellow	Red	Yellow	Yellow
ELPI	Yellow	Red	Yellow	Yellow
PM _{2.5}	Yellow	Red	Yellow	Yellow
Sputum CNT/F	Yellow	Yellow	Yellow	Yellow
Any CNT/F	Yellow	Blue	Yellow	Yellow
CNT/F duration	Yellow	Yellow	Yellow	Red

CNT/F and Sputum Biomarkers

Cardiovascular

Variable	Fibrinogen	ICAM-1	PAI-1	t-PA	VCAM-1	vWF
Inhalable EC	Red	Yellow	Yellow	Yellow	Red	Yellow
Respirable EC	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Total CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Single CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F <1 μm	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F <2 μm	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F <5 μm	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F <10 μm	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CPC	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
ELPI	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
PM _{2.5}	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Sputum CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Any CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F duration	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow

Blood Biomarker Factor Loadings

Biomarker	Factor								
	1	2	3	4	5	6	7	8	9
<i>Cancer/Fibrosis</i>									
MUC-1/KL-6	-0.04	0.20	-0.77	-0.02	0.04	0.05	0.18	-0.09	-0.03
MMP-2	-0.29	0.29	-0.10	0.27	-0.12	0.20	0.45	0.40	0.00
MMP-7	0.07	0.27	-0.19	-0.10	0.70	0.06	0.24	0.11	-0.13
MMP-9	0.14	-0.02	-0.03	0.03	0.53	-0.04	-0.06	0.54	0.18
SPP-1	-0.08	-0.07	0.00	0.61	-0.11	-0.05	-0.16	0.24	0.37
TIMP-1	0.20	0.30	0.02	0.56	0.20	0.32	0.12	-0.15	-0.22
<i>Inflammation</i>									
α-2-M	-0.09	-0.54	-0.38	-0.12	0.03	-0.02	0.23	0.09	0.48
Apo-AI	-0.07	-0.24	0.17	0.04	0.19	0.11	0.75	-0.20	0.26
Apo-AII	-0.01	0.28	0.75	0.12	-0.02	0.13	0.13	-0.30	0.02
CRP	0.73	0.12	0.21	-0.15	0.03	0.34	-0.01	-0.06	-0.15
C3	0.65	0.14	0.25	-0.08	0.19	0.16	0.10	0.19	0.07
IL-1 β	0.32	-0.02	-0.15	-0.01	0.37	0.00	0.29	-0.08	0.38
IL-6R-β	0.11	0.29	0.19	0.60	0.00	-0.28	0.24	0.09	0.15
IL-8	0.23	0.13	0.04	0.07	0.71	0.14	-0.04	0.01	0.02
IL-18	0.62	0.27	0.00	0.27	0.03	-0.15	-0.02	-0.03	0.00
MDC	-0.08	0.59	0.10	-0.12	0.21	0.18	-0.27	-0.01	0.23
<i>Oxidative Stress</i>									
8-OHdG	0.05	0.09	0.75	0.08	-0.05	0.19	-0.01	-0.02	-0.18
GPx	0.14	0.01	-0.27	-0.22	-0.03	-0.17	0.63	0.17	-0.03
MPO	-0.06	0.06	-0.08	0.24	0.05	-0.03	0.03	0.82	-0.13
SOD	-0.07	0.13	-0.04	0.03	-0.02	0.02	0.07	-0.06	0.78
<i>Cardiovascular/Coagulation</i>									
EDN1	-0.09	0.02	0.06	0.45	0.42	-0.18	-0.28	-0.04	-0.01
Fibrinogen	0.46	0.09	0.08	0.00	0.14	0.71	0.17	0.26	0.10
ICAM-1	0.65	0.03	-0.20	0.11	0.15	-0.11	-0.03	-0.09	-0.06
PAI-1	0.25	0.72	0.07	0.13	0.19	0.11	0.13	0.20	0.08
t-PA	0.29	0.76	-0.09	0.03	0.08	0.10	-0.03	-0.04	-0.03
VCAM-1	0.09	-0.09	0.09	0.75	-0.01	0.17	-0.08	0.19	-0.14
vWF	-0.12	0.27	0.22	0.06	0.05	0.79	-0.12	-0.17	-0.01

67% of variance explained

Colored loadings have largest magnitudes for each biomarker

CNT/F and Blood Biomarker Factors

Key

	Positive association p-value < 0.05
	p-value ≥ 0.05
	Inverse association p-value < 0.05

Variable	Factor								
	1	2	3	4	5	6	7	8	9
Inhalable EC	Yellow	Yellow	Yellow	Yellow	Yellow	Blue	Yellow	Yellow	Blue
Respirable EC	Yellow	Yellow	Blue	Yellow	Yellow	Blue	Yellow	Yellow	Blue
Total CNT/F	Red	Yellow	Red	Yellow	Red	Blue	Yellow	Yellow	Blue
Single CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Blue	Yellow	Yellow	Blue
CNT/F <1 μm	Yellow	Yellow	Yellow	Yellow	Yellow	Blue	Yellow	Yellow	Blue
CNT/F <2 μm	Yellow	Yellow	Yellow	Yellow	Yellow	Blue	Yellow	Yellow	Blue
CNT/F <5 μm	Red	Yellow	Yellow	Yellow	Red	Blue	Yellow	Yellow	Blue
CNT/F <10 μm	Red	Yellow	Red	Yellow	Red	Blue	Yellow	Yellow	Blue
CPC	Yellow	Yellow	Blue	Yellow	Yellow	Yellow	Red	Red	Yellow
ELPI	Red	Yellow	Blue	Yellow	Yellow	Yellow	Red	Red	Yellow
PM _{2.5}	Yellow	Red	Yellow	Yellow	Yellow	Yellow	Red	Red	Yellow
Sputum CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Any CNT/F	Red	Yellow	Red	Red	Yellow	Yellow	Blue	Yellow	Yellow
CNT/F duration	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Blue

CNT/F and Blood Biomarkers

Variable	Fibrosis					
	KL-6	MMP-2	MMP-7	MMP-9	SPP-1	TIMP-1
Inhalable EC	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Respirable EC	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Total CNT/F	Yellow	Yellow	Yellow	Red	Yellow	Red
Single CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F <1 μm	Yellow	Yellow	Yellow	Red	Yellow	Yellow
CNT/F <2 μm	Yellow	Yellow	Yellow	Red	Yellow	Yellow
CNT/F <5 μm	Yellow	Yellow	Yellow	Red	Yellow	Yellow
CNT/F <10 μm	Yellow	Yellow	Yellow	Red	Yellow	Red
CPC	Red	Yellow	Red	Yellow	Yellow	Red
ELPI	Red	Yellow	Yellow	Yellow	Yellow	Red
PM _{2.5}	Yellow	Blue	Yellow	Yellow	Yellow	Yellow
Sputum CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Any CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Red
CNT/F duration	Yellow	Red	Yellow	Yellow	Yellow	Yellow

CNT/F and Blood Biomarkers

Inflammation

Variable	α -2-M	Apo-AI	Apo-AII	CRP	C3	Eotaxin-1	IL-1 β	IL-6R- β	IL-8	IL-10	IL-18	MDC
Inhalable EC	Red	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Respirable EC	Yellow	Red	Blue	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Total CNT/F	Yellow	Yellow	Yellow	Yellow	Blue	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Single CNT/F	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F <1 μ m	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F <2 μ m	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F <5 μ m	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CNT/F <10 μ m	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
CPC	Yellow	Yellow	Yellow	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Blue
ELPI	Yellow	Yellow	Yellow	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Blue
PM _{2.5}	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Red	Yellow	Yellow	Yellow	Yellow
Sputum CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Blue
Any CNT/F	Yellow	Yellow	Red	Yellow	Blue	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Blue
CNT/F duration	Yellow	Yellow	Yellow	Yellow	Yellow	Blue	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow

CNT/F and Blood Biomarkers

Variable	Oxidative Stress			
	8-OHdG	GPx	MPO	SOD
Inhalable EC	Red	Red	Yellow	Yellow
Respirable EC	Yellow	Red	Yellow	Yellow
Total CNT/F	Yellow	Red	Yellow	Blue
Single CNT/F	Yellow	Red	Yellow	Yellow
CNT/F <1 μm	Yellow	Red	Yellow	Yellow
CNT/F <2 μm	Yellow	Red	Yellow	Blue
CNT/F <5 μm	Yellow	Red	Yellow	Blue
CNT/F <10 μm	Yellow	Red	Yellow	Blue
CPC	Blue	Red	Red	Yellow
ELPI	Blue	Red	Red	Yellow
PM _{2.5}	Yellow	Red	Red	Yellow
Sputum CNT/F	Yellow	Yellow	Yellow	Yellow
Any CNT/F	Red	Blue	Yellow	Yellow
CNT/F duration	Yellow	Red	Yellow	Yellow

CNT/F and Blood Biomarkers

Cardiovascular

Variable	EDN1	Fibrinogen	ICAM-1	PAI-1	t-PA	VCAM-1	vWF
Inhalable EC	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Blue
Respirable EC	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Blue
Total CNT/F	Red	Blue	Red	Yellow	Yellow	Red	Blue
Single CNT/F	Yellow	Red	Yellow	Yellow	Yellow	Yellow	Blue
CNT/F <1 μm	Yellow	Red	Yellow	Yellow	Blue	Yellow	Blue
CNT/F <2 μm	Yellow	Red	Yellow	Yellow	Blue	Yellow	Blue
CNT/F <5 μm	Red	Yellow	Red	Yellow	Yellow	Red	Blue
CNT/F <10 μm	Red	Yellow	Red	Yellow	Yellow	Red	Blue
CPC	Yellow	Yellow	Yellow	Red	Yellow	Yellow	Yellow
ELPI	Blue	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
PM _{2.5}	Yellow	Yellow	Yellow	Red	Yellow	Yellow	Yellow
Sputum CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Any CNT/F	Yellow	Yellow	Yellow	Yellow	Yellow	Red	Yellow
CNT/F duration	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow

CNT/F and Chest Symptoms

Variable	Chest Symptoms	Respiratory Allergy
Inhalable EC	Yellow	Red
Respirable EC	Yellow	Yellow
Total CNT/F	Yellow	Yellow
CPC	Yellow	Yellow
ELPI	Yellow	Yellow
PM _{2.5}	Yellow	Yellow
Sputum CNT/F	Yellow	Yellow
CNT/F duration	Yellow	Red

CNT/F and Lung Function

Variable	FVC	FEV1/FVC	FEF25-75	PEF
Inhalable EC				
Respirable EC				
Total CNT/F				
Sputum CNT/F				
CNT/F duration				

CNT/F and RBP and RHR

Variable	Systolic Diastolic Heart		
	BP	BP	Rate
Inhalable EC	Yellow	Yellow	Red
Respirable EC			Red
Total CNT/F	Yellow	Yellow	Yellow
Sputum CNT/F			Yellow
CNT/F duration			Blue

CNT/F and CBC Components

Variable	Leukocytes	Neutrophils	Lymphocytes
Inhalable EC			
Respirable EC			
Total CNT/F			
Sputum CNT/F			
CNT/F duration			

Variable	Monocytes	Platelets	Hemoglobin	Hematocrit
Inhalable EC				
Respirable EC				
Total CNT/F				
Sputum CNT/F				
CNT/F duration				

Conclusions

- Findings support associations between occupational CNT/F exposure and early human health effects
- Results need to be confirmed in other exposed populations
- Consider recommended exposure limits based on inhalable CNT/F

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