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Immunological and Respiratory Effects among Workers Who Handle Engineered Nanoparticles at work

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GROUP OF EIGHT AUSTRALIA

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DECLARATION OF INTERESTS

- This research was funded by a project grant from the Australian National Health and Medical Research Council (NHMRC)
- No competing interests to declare

BACKGROUND

- Engineered nanoparticles being increasingly used as an ‘add on’ material in a wide range of processes
- Less than 100nm in diameter
- Can easily enter the body through the respiratory tract, skin and gastrointestinal tract
- High surface to weight ratio means they can adsorb other substances and deliver these to target organs

Animal studies

- Can cause inflammation and immunosuppression in studies in mice
- Increased serum inflammatory markers: several interleukins and tumour necrosis factor
- Trigger production of reactive oxygen species
- Damage to cell membranes and DNA
- Animal studies diff exposure profile to workers
- Some preliminary findings in human studies of pulmonary effects, inflammatory changes, oxidative stress, cytokines

Study aims

- Quantify ENP exposure in workers handling ENPs
- Investigate changes in:
  - Respiratory function
  - Inflammatory markers
- Over a shift and over a working week

METHODS 1

- Panel study – Monash Ethics approval
- Recruit workers from research laboratories – difficulty identifying other ENP workplaces
- Making, mixing, spraying ENPs – variable times
- Control workers from other labs – no work with ENP
- Data collected at start of first shift of the week, end of first shift and at the end of the working week
- Exposure measured for a sample of participants using Nanotracer:
  - Continuous real time monitor

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METHODS 2

- Human data collection:
  - Questionnaire, including resp questionnaire
  - Height and weight
  - Skin prick test: 4 common allergens to test atopy
  - FVC and FEV_1
  - Fraction of exhaled nitric oxide (FeNO)
  - Blood for C-reactive protein and blood counts
  - Several serum cytokines and mediators (eg Ils, TNFa and soluble serum proteins)

RESULTS 1 – Exposure groups

- 89 subjects recruited
- The handling of ENPs was very variable and unpredictable in the 8 research laboratories.
- For the analyses at each stage, subjects were grouped into:
  1. Those who had ever (n=34) or never (n=55) handled ENPs.
  2. Those who handled them on Monday (n=19), those who had not (n=69)
  3. Those who handled them during the week of data collection (n=27) and those who had not (n=57).

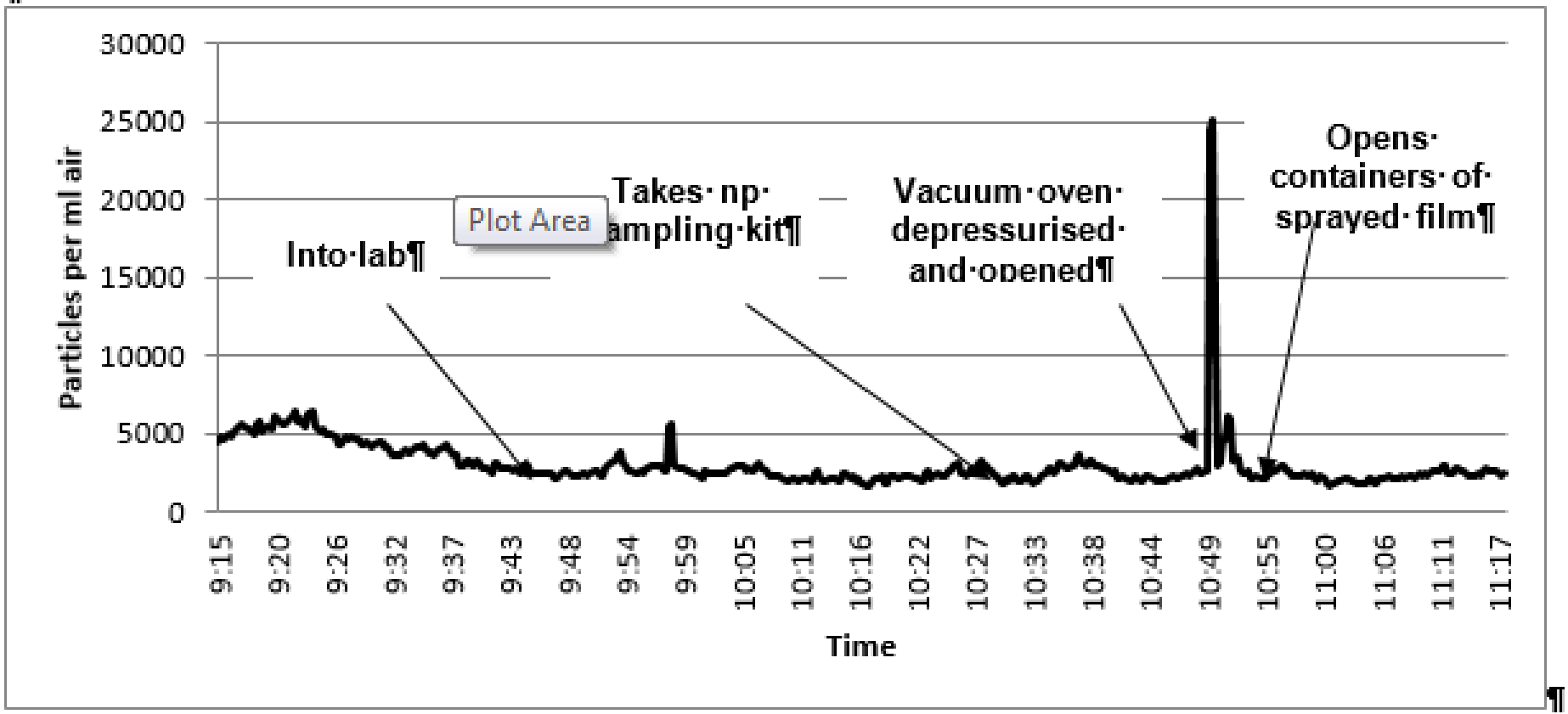
- NanoTracer measurements appeared anomalous!

Table 1: Summarised personal sampling exposure data from NanoTracer

Site	Non-ENP handling Activity			ENP Handling Activity			Ambient at Lab/Office where exposure measured		
	Period mins	Count particles /ml air	Mean Diameter nm	Period mins	Count particles /ml air	Mean Diameter nm	Period mins	Count particles /ml air	Mean Diameter nm
Area 1	229	4663	61	42	1964	58	105	9650	n/a
Area 2	268	12554	46	75	9061	54	119	10722	42
Area 3	204	4227	78	727	3644	68	47	22620	n/a
Area 4	150	11699	46	295	8067	40	64	13129	n/a
Area 5	78	5507	44	128	5035	46	64	13129	n/a
Area 6	241	6073	36				326	31571	n/a
Area 7	237	14090	41				4	8434	35

NanoTracer can’t distinguish between ENPs and other nanoparticles

Supplementary·Figure·2:·Nanotracer·graphs·of·particle·count·against·the·period·of·sampling·during·work·in·the·laboratory.··Vacuum·oven·opening·resulted·in·large·spike·in·nanoparticles¶



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BASELINE CHARACTERISTICS (morning of first shift)

- Similar demographics and medical status, but ENP group less likely to be asthmatic; 25% vs 3% and more likely male; 68% vs 29%
- CRP lower in the ENP group (0.3 vs 0.8)
- No sig differences at baseline between the 2 groups on any other testing parameters: spirometry, FeNO, blood counts, cytokines

CHANGES OVER FIRST SHIFT

- A significant increase in those handling ENPs over controls for serum CD40 and TNFR2, but not CD62P:

Cytokines (pg/ml)		N = 50	N = 19	
sCD40	Monday am	3145 [1634]	3417 [1888]	
	Monday pm	2773 [2017]	4685 [2217]	**1819 [557, 3050]**
sCD62P	Monday am	5022 [3092]	5554 [2709]	
	Monday pm	4378 [2736]	5643 [2624]	586 [-548, 1721]
sTNFR2	Monday am	2746 [1119]	2804 [1056]	
	Monday pm	2495 [1267]	3425 [1438]	**1167 [418, 1916]**

- When removed asthmatics, similar pattern, but weaker
- Similar pattern for non-atopics, but not atopics
- No sig changes in spiro, FeNO, blood counts

CHANGES OVER WEEK (Mon morning to Fri afternoon)

- Similar findings as for increases in CD40 and TNFR2 over the first day, but in addition change in serum CD62P was sig higher in ENP workers over controls over the week
- Similar patterns with non-asthmatics and atopic status as found over first shift
- No sig differences in any other measures

For all analyses:

- pro-inflammatory cytokines and inflammatory mediators such as TNFα, IL-6, IL-8 and GM-CSF were low or non-detectable in all participant samples

Discussion and conclusions

- Changes consistent with an anti-inflammatory and suppressive effect on immune response
- Increases much smaller than found in cancer patients
- Some features similar findings for previous studies of air pollution NPs (nor ENPs)
- Asthmatic and atopic status may play a role
- Clinical significance and longer term impact of these changes uncertain
- No changes in other biological parameters found
- Limitations: small size, exposure misclassification

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Questions?