

Table 1. Studies providing empirical evidence for the relationship between KE1 (Event 1496) and KE2 (Event 1497). +: Severity of Response. References available in main KER page.

Stressor (Reference)	<i>In vitro/ in vivo/ ex vivo</i>	Species/cell line	Exposure Conditions	KE1 (Event 1496) Increased, secretion of pro- inflammatory and pro-fibrotic mediators	KE2 (Event 1497) Increased, recruitment of pro-inflammatory cells	
Nanosized silica (Schremmer et al., 2016)	<i>In vitro</i>	NR8383 rat alveolar macrophages	16 µg/cm ² for 1, 4, 16 h	Pro-inflammatory mediators using the supernatants obtained at different time points. (CCL4, CXCL1, CXCL3, TNF-α)	Chemotaxis using the supernatants obtained at different time points.	
				1 h: 4 h: + 16 h: ++	1 h: 4 h: + 16 h: ++	
Particulate matter PM _{2.5} (Wang et al., 2019)	<i>In vitro</i>	Co-culture: A549 +THP- 1+EA.hy926 cells	20, 60, 180 µg/ml for 24 h	Increased IL-6, IL-8 and TNF-α	Increased MMP9, ICAM-1, and CAV-1 mRNA expression	
				60: ++ 180: +++	20: + 60: ++ 180: +++	
Multi-walled carbon nanotubes (Ma et al., 2016)	<i>In vivo</i>	Male BALB/c mice	0.5, 1, 2, 4 mg/Kg intravenous injection Evaluation: 2 days post- exposure	Increased IL-6 and TNF-α	Increased the number of white blood cells, lymphocytes, and neutrophils	
				0.5: + 1: ++ 2: ++ 4: +++	0.5: 1: 2: 4: +++	
Multi-walled carbon nanotubes (Porter et al., 2020)	<i>In vivo</i>	Male C57BL/6J mice	2.5, 10, 40 µg/mouse oropharyngeal aspiration Evaluation: 1, 7 days post- exposure	Increased cathepsin, IL-1β, IL-18 (Day 1)	Increased number of polymorphonuclear cells (Day 1, Day 7)	
				40: Increased cathepsin, IL-1β, IL-18	Day 1 2.5: + 10: ++ 40: +++	Day 7 2.5: 10: +++ 40: ++++

Oleoresin C Spray (Patowary et al., 2020)	<i>In vivo</i>	Female Wistar rats	2%, 6%, 10% spray via whole body inhalation (single 20 min exposure) Evaluation: 1, 3, 24 h post-exposure	1 h TNF- α 2%: +++	3 h TNF- α 6%: ++	24 h TNF- α 10%: +	Total cells in BALF:		
				IL-1 10%: +	IL-1 10%: +	IL-1 10%: +	1 h 2%: +	3 h 2%: + 6%: ++ 10%: ++	24 h 2%: + 6%: ++ 10%: ++
Carbon nanoparticles (Chen et al., 2016)	<i>In vivo</i>	Female C57BL/6J mice	20 μ g/mouse intratracheal instillation Evaluation: 3-24 h post-exposure	Increase cytokine release			Total cell numbers in BALF		
				CXCL1 3 h: + 6 h: + 12 h: +++ 18 h: ++ 24 h: +	CXCL2 3 h: ++ 12 h: ++ 24 h: +	CXCL2 12 h: +++ 18 h: +++	6 h: + 12 h: ++ 24 h: +++		
Nickel oxide nanoparticles (Lee et al., 2016)	<i>In vivo</i>	Female Wistar rats	200 μ m ² /rat intratracheal instillation Evaluation: 24-96 h post-exposure	24 h: Increased CINC3 48 h: 72 h: Increased eotaxin 96 h:			24 h: + neutrophils 48 h: ++ neutrophils 72 h: ++ neutrophils/eosinophils 96 h: +++ neutrophils/eosinophils/macrophages		
Crystalline silica (Porter et al., 2002)	<i>In vivo</i>	Male Fischer 344 rats	15 mg/m ³ inhalation (6h/day, 5 days/week) Evaluation: 5 - 116 days post-exposure	Increased BALF inflammatory mediators (IL-1; TNF- α) Day 10: IL-1 + Day 16: Day 20: Day 30: TNF- α + /IL-1 ++ Day 41: IL-1 + Day 79: TNF- α ++/IL-1 +++ Day 116: TNF- α ++/IL-1 ++++			Polymorphonuclear cells in BALF: Day 5: + Day 10: + Day 16: + Day 20: + Day 30: + Day 41: ++ Day 79: +++ Day 116: ++++		Neutrophils in BALF: Day 5: + Day 10: + Day 16: + Day 20: + Day 30: + Day 41: + Day 79: + Day 116: +
Carbon black nanoparticles	<i>In vivo</i>	Female C57BL/6 mice	162 μ g/mouse intratracheal instillation	Increased gene expression 3 h: IL-6, Ccl2			Recruitment of cells 3 h: + Neutrophils		

(Husain et al., 2015)			Evaluation: 3h – 42 days post-exposure	Day 1: Cxcl2, Ccl2 Day 2: Day 3: IL-17, IL-33 Day 4: Day 5: Day 14: Cd2 Day 42: Cxcl5	Day 1: + Neutrophils Day 2: + Neutrophils Day 3: + Neutrophils Day 4: +++ Neutrophils, eosinophils, lymphocytes and macrophages Day 5: ++++ Neutrophils, macrophages and lymphocytes Day 14: + Neutrophils Day 42: + Neutrophils, macrophages
Multi-walled carbon nanotubes (Poulsen et al., 2013)	<i>In vivo</i>	Female C57BL/6 mice	18 – 162 µg/mouse Intratracheal instillation Evaluation: 24 h post-exposure	Increased gene expression (Cxcl1, IL-6, Mt2, Saa1, Saa3) 18: + 54: ++ 162: +++	Increased pro-inflammatory cells 18: + Neutrophils 54: ++ Neutrophils 162: +++ Neutrophils
Coated zinc oxide nanoparticles (Hadrup et al., 2019)	<i>In vivo</i>	Female C57BL/6J mice	11, 33, 100 µg/Kg intratracheal instillation Evaluation: 1-28 days post-exposure	Saa3 mRNA levels in lung Day 1 Day 3 Day 28 33: +++ 100: +++	Neutrophils in BALF Day 1 Day 3 Day 28 11: + 33: ++ 100: +++
Titanium dioxide nanoparticles (Rahman et al., 2017)	<i>In vivo</i>	Female C57BL/6 mice	18, 54, 162, 486 µg/mouse intratracheal instillation Evaluation: 1-28 days post-exposure	Increased gene expression associated with inflammation Day 1 Day 28 18: ++ 54: ++ 162: ++ 468: ++ 18: + 54: + 162: + 468: +	BALF cell counts Day 1 Day 28 18: + 54: ++ 162: +++ 468: ++++ 18: + 54: ++ 162: +++ 468: ++++
Polyhexamethyl guanidine phosphate (Song et al., 2014)	<i>In vivo</i>	Male C57BL/7 mice	0.3, 0.9, 1.5 mg/Kg Single intratracheal instillation 7-14 days post-exposure	Increased IL-1 β , IL-6, CXCL1 levels Day 7 Day 14 0.9: ++ 1.5: +++ 0.9: ++ 1.5: +++	Increased MCP-1, MMP2, MMP12 mRNA expression Day 7 Day 14 0.3: + 0.9: ++ 1.5: ++ 0.3: + 0.9: ++ 1.5: ++

Carbon black nanoparticles (Bourdon et al., 2012)	<i>In vivo</i>	Female C57BL/6 mice	0.018, 0.054, 0.162 mg intratracheal instillation Evaluation: 1-28 days post-exposure	Saa3 mRNA expression			BALF cell counts						
				Day 1 0.018: +++ 0.054: ++++ 0.162: +++++	Day 3 0.018: ++ 0.054: +++ 0.162: +++++	Day 28 0.018: + 0.054: ++ 0.162: +++	Day 1 0.018: + 0.054: ++ 0.162: +++	Day 3 0.018: + 0.054: ++ 0.0162: +++	Day 28 0.018: + 0.054: ++ 0.0162: ++				
Quantum dot 705 (PEG or COOH coated) (Ho et al., 2013)	<i>In vivo</i>	Male ICR mice	12 and 60 µg/mouse intratracheal instillation of QD705-PEG or QD705-COOH Evaluation: 2, 17 and 90 days post-exposure	mRNA levels of gene expression (TNF-α, IL-1β, IL-6, CXCL1, CCL2, CCL1, CCL17, CXCL13)			BALF cell counts						
				Day 2 60: +	Day 17 12: ++ 60: +++	Day 90 60: ++	Day 2 60: +	Day 17 12: + 60: ++	Day 90 60: ++				
Nickel oxide (Morimoto et al., 2010)	<i>In vivo</i>	Male Wistar Rats	0.33, 0.66 mg/Kg intratracheal instillation Evaluation: 3 days, 1 week, 3 months, 6 months post-exposure	Concentration of MCP-1 (BALF) and IL-1β					Alveolar macrophage cells in BALF				
				Day 3 0.33: ++	Week 1 0.33: ++ 0.66: +	Month 1 0.33: ++ 0.66: +++	Month 3 0.33: +	Month 6	Day 3 0.33: + 0.66: +	Week 1 0.33: + 0.66: +	Month 1 0.33: + 0.66: ++	Month 3 0.33: ++ 0.66: +++	Month 6
Bleomycin and carbon black nanoparticles (Kamata et al., 2011)	<i>In vivo</i>	Female C57BL/6J mice	Bleomycin 20 µg/mouse and carbon black nanoparticles 10 µg/mouse intratracheal instillation Evaluation: 2 – 21 days post-exposure	Concentration of IL-6 and CCL2 in BALF				Total cells, macrophages, and lymphocytes in BALF					
				Day 2 ++	Day 7 +++	Day 14 +	Day 21	Day 2 +	Day 7 ++	Day 14 +++	Day 21 ++		

BALF: Bronchoalveolar lavage fluid.

CAV-1: Caveolin 1.

CCL: C-C motif chemokine ligand.

CINC3: Cytokine-Induced neutrophil chemoattractant 3.

CXCL: C-X-C motif chemokine ligand.

IL: Interleukin.

ICAM-1: Intercellular adhesion molecule 1.

MCP: Monocyte chemoattractant protein.

MMP: Matrix metalloproteinase.

Mt2: Metallothionein-2.

Saa: Serum Amyloid A3.

TNF- α : Tumor necrosis factor alpha.