

Table 1. Studies providing empirical evidence for the relationship between KE2 (Event 1497) and KE3 (Event 1498).

+: Severity of Response. References available in main KER page.

Stressor (Reference)	<i>In vitro/in vivo</i>	Species/Cell line	Exposure conditions	KE2 (Event 1497) Increased, recruitment of pro-inflammatory cells			KE3 (Event 1498) Loss of alveolar capillary membrane integrity	
				1 h	6 h	24 h	24 h	
Polyhexamethylene guanidine phosphate (Kim et al., 2016)	<i>In vitro</i>	Calu-3, THP-1 and HMC-1 cells (Bronchial ALI co-culture)	2.2, 4.4, 8.8, 17.6 mg/mL Incubation for 1, 6, 24 h	Chemoattractant cytokine IL-8			Disruption of the epithelial airway barrier (Paracellular flux %, transepithelial electrical resistance)	
				2.2: + 4.4: ++ 8.8: ++ 17.6: ++	2.2: + 4.4: ++ 8.8: +++ 17.6: ++++	2.2: + 4.4: ++ 8.8: ++++ 17.6: ++++	2.2: 4.4: 8.8: + 17.6: ++	
Silica nanoparticles (Kasper et al., 2011)	<i>In vitro</i>	Co-culture, microvascular endothelial cell line and the human lung adenocarcinoma cell line.	6, 60, 600, 6000 µg/mL 4 h exposure, 4 h exposure + 20 h recovery	Increased sICAM-1, IL-6, IL-8			Decreased transepithelial electrical resistance	
				4 h exposure + 20 h recovery			4 h exposure	
				6: + 60: ++ 600: +++ 6000: +++		6: + 60: ++ 600: +++ 6000: ++++		
fMLP (N-formylmethionyl-leucyl-phenylalanine) (Gautam et al., 1998)	<i>Ex vivo</i>	Bovine aorta endothelial cells (BAEC)	10 ⁻⁷ M lower compartment for 0, 10, 20, 30, 40, 50 min	Transmigration of PMN			Albumin clearance	Decreased endothelial cells resistance
				0 min: + 10 min: + 20 min: ++ 30 min: ++ 40 min: +++ 50 min: +++			0 min: + 10 min: + 20 min: ++ 30 min: ++ 40 min: +++ 50 min: +++	0 min: + 10 min: ++ 20 min: ++ 30 min: ++
Multi-walled carbon nanotubes (Porter et al., 2013)	<i>In vivo</i>	Male mice C57BL/6J	10 mg/m ³ aerosol inhalation 5h/day for 2, 4, 8, 12 days	Increased PMN	Neutrophil chemoattractant	Whole lung fluid		

			Evaluation: post-exposure	Day 2: + Day 4: + Day 8: ++ Day 12: ++	Day 2: + Day 4: ++ Day 8: +++ Day 12: +++	Albumin concentration		LDH activity								
						Day 2: + Day 4: ++ Day 8: +++ Day 12: +++		Day 2: + Day 4: ++ Day 8: +++ Day 12: +++								
Crystalline silica (Umbright et al., 2017)	<i>In vivo</i>	Male Fischer 344 rats	15 mg/m ³ inhalation, 6h/day, 5 days/week for 3, 6, 12 weeks Evaluation: post-exposure	Increased PMN		Albumin concentration-BALF		BALF LDH activity								
				Week 3: + Week 6: ++ Week 12: +++		Week 3: Week 6: ++ Week 12: +		Week 3: ++ Week 6: ++ Week 12: ++								
Paraquat (Shinozaki et al., 1992)	<i>In vivo</i>	Sheep	5 mg/Kg intramuscular injection Evaluation: 1, 2, 3 weeks post-exposure	Number of granulocytes		Alveolar wall thickening		Lung malondialdehyde								
				Week 1: + Week 2: + Week 3: ++		Week 1: Week 2: Week 3: +++		Week 1: Week 2: Week 3: +++								
DQ12 particles (Arras et al., 2001)	<i>In vivo</i>	Transgenic Tg5 mice expressing high levels of IL- 9. WT FVB mice C57BL6/J	1, 5 mg intratracheal instillation. Evaluation: 2, 4 months post-exposure	Increased PMN in BALF		LDH content in BALF		Proteins in BALF								
				Month 2 1: + 5: ++		Month 4 1: + 5: ++		Month 2 1: + 5: ++		Month 4 1: + 5: ++		Month 2 1: + 5: ++	Month 4 1: + 5: ++			
CeO ₂ nanoparticles (Morimoto et al., 2015)	<i>In vivo</i>	Male Fischer 344 rats	0.2 mg (0.8 mg/kg), 1 mg (4 mg/Kg) intratracheal instillation Evaluation: 3 days (D), 1 week (W), 1, 3, 6 months (M) post-exposure	Total cell counts in BALF					LDH activity in BALF							
				3D 0.2: 1:	1W 0.2: 1: +++	1 M 0.2: 1: ++	3M 0.2: 1: ++	6M 0.2: 1:	3D 0.2: +++ 1: +++++	1W 0.2: ++ 1: +++	1 M 0.2: + 1: ++	3M 0.2: + 1: +	6M 0.2: + 1: +			
				2, 10 mg/m ³ Inhalation, 6h per day, 5 days/week, 4 weeks Evaluation: 3 days, 1, 3 months post-exposure					Total cell counts in BALF					LDH activity in BALF		
					Day 3 2: ++ 10: +++		Month 1 2: 10:		Month 3 2: 10: ++		Day 3 2: +++ 10: +++++		Month 1 2: ++ 10: +++		Month 3 2: + 10: ++	

Nickel nanoparticles (Mo et al., 2019)	<i>In vivo</i>	Male C57BL/6 mice	10, 20, 50, 100 µg/mouse intratracheal instillation	Neutrophil count in BALF		TBARS 8-OHdG level	LDH activity	Total protein in BALF
			Evaluation: 3 days post-exposure	10: + 20: + 50: +++ 100: ++	10: 20: 50: 100:	10: + 20: + 50: +++ 100: ++	10: + 20: + 50: +++ 100: +	
			50 µg/mouse intratracheal instillation	Neutrophil count in BALF		*3 days post-exposure	LDH activity	Total protein in BALF
			Evaluation: 1, 3, 7, 14, 28, 42 days post-exposure	Day 1: ++ Day 3: +++ Day 7: + Day 14: + Day 28: + Day 42: +	Increased levels of TBARS and 8-OHdG in lung tissues	Day 1: + Day 3: +++ Day 7: ++ Day 14: + Day 28: + Day 42: +	Day 1: + Day 3: +++ Day 7: ++ Day 14: + Day 28: + Day 42: +	
Radiation (Park et al., 2009)	<i>In vivo</i>	Sprague-Dawley rats	Right lung 20 Gray (Gy) of radiation	Increase cell count in BALF		Total protein in BALF		
			Evaluation: 3, 7, 14, 28, 56 days post-exposure	Day 3: Day 7: Day 14: + Day 28: + Day 56: +++	Day 3: Day 7: - Day 14: + Day 28: ++++ Day 56: +			
Ricin (Sapoznikov et al., 2019)	<i>In vivo</i>	Female CD-1 mice	Crude ricin (50 µl; 7 µg/Kg diluted in PBS) administered intranasally	Neutrophil count increase		Evans blue dye extravasation	Decrease Vascular Endothelial-cadherin, claudin 18, claudin 5, connexin 43 and occludin protein expression	
			Evaluation: 3, 6, 24, 48, 72 Hours post-exposure	24 h: + 48 h: ++ 72 h: +++	6 h: + 24 h: ++ 48 h: +++ 72 h: +++	3 h: +++ 6 h: +++ 24 h: +++ 48 h: +++ 72 h: +		
Cobalt nanoparticles (Wan et al., 2017)	<i>In vivo</i>	Female or male gpt delta transgenic mice (C57BL/6 background)	50 µg/mouse intratracheal instillation	CXCL1/KC In BALF	Neutrophils in BALF	LDH activity in BALF	Protein content in BALF	8-OHdG levels in lung tissue
			Evaluation: 1, 3, 7, 28 days, 4 months post-exposure	Day 1: +++ Day 3: +++ Day 7: +++ Day 28: +	Day 1: +++ Day 3: +++ Day 7: ++ Day 28: +	Day 1: +++ Day 3: +++ Day 7: +++ Day 28: ++	Day 1: ++ Day 3: +++ Day 7: ++ Day 28: +	Month 4: ++

IL: Interleukin.

PMN: Polymorphonuclear cells.

sICAM: Soluble intercellular adhesion molecule 1.

BALF: Bronchoalveolar lavage fluid.

LDH: Lactate dehydrogenase.

TBARS: Thiobarbituric acid reactive substances.

8-OHdG: 8-hydroxy-2-deoxyguanosine.

CXCL1/KC: C-X-C motif chemokine ligand 1/keratinocyte-derived chemokine.