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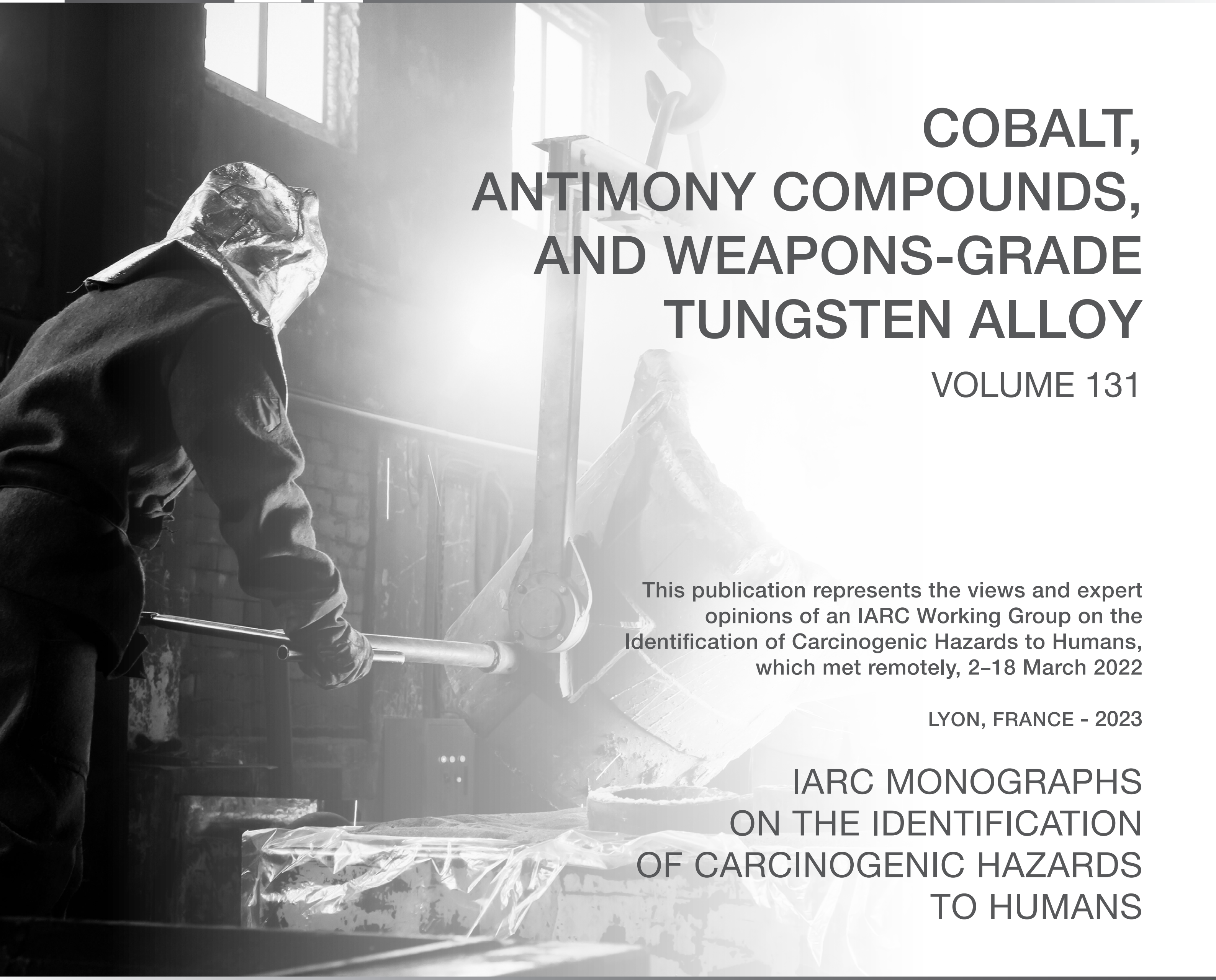

COBALT, ANTIMONY COMPOUNDS, AND WEAPONS-GRADE TUNGSTEN ALLOY

VOLUME 131

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met remotely, 2–18 March 2022

LYON, FRANCE - 2023

IARC MONOGRAPHS
ON THE IDENTIFICATION
OF CARCINOGENIC HAZARDS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

Table S4.16 Acute pro-inflammatory effects in human cells in vitro exposed to cobalt

End-point	Tissue, cell type or line	Results[a] (without metabolic activation)	Direction of response	Exposure concentration(s)	Comments	Reference
Cobalt(II) chloride ($CoCl_2$)						
TNFα	Human trophoblasts	+	↑	250 µM	Primary trophoblasts isolated from normal placentas. ↑ TNFα protein levels after 48 h exposure (ELISA).	Ma et al. (2011)
IL-6, IL-1β, and TNFα	Human keratinocyte cell line HaCaT	+	↑	500 µM	↑ IL-6, IL-1β, and TNFα protein levels after 24 h exposure (ELISA). ↑ mRNA expression levels after 6, 12, and 24 h exposure for IL-1β and TNFα, and after 3, 6, 12, and 24 h for IL-6 (RT-PCR).	Sun et al. (2015)
IL-6, IL-1β, IL-8, COX-2, and PGE2	Human keratinocyte cell line HaCaT	+	↑	500 µM	↑ IL-6, IL-1β, and IL-8 protein levels after 24 h exposure (ELISA). ↑ COX-2 (WB) and PGE2 (ELISA) protein levels after 6 h exposure.	Yang et al. (2011b)
IL-6, IL-8, and COX-2	Human keratinocyte cell line HaCaT	+	↑	400 and 500 µmol/L	↑ IL-6 and IL-8 protein levels after 24 h exposure to 400 and 500 µmol/L, respectively (ELISA). ↑ COX-2 protein levels after 1–3 h exposure to 500 µmol/L (WB).	Yang et al. (2011a)
IL-8 and MCP-1	HPMVECs HDMVECs HDMVEC-immortalized cells HBECs HPAECs	+ + + + –	↑ ↑ ↑ ↑ NA	0.5 and 1 mM	↑ IL-8 protein levels after 24 h exposure (0.5 mM) of HPMVECs (ELISA). ↑ MCP-1 and IL-8 mRNA expression levels after 1 h exposure (1 mM) of HPMVECs, HDMVECs, and HBECs, (but not HPAECs), and of HDMVEC-immortalized cells (0.5 and 1 mM) (RPA).	Kim et al. (2006b)
MCP-1	Human RASFs	+	↓	10 µM	Primary cells collected from patients with rheumatoid arthritis. ↓ MCP-1 mRNA expression levels after 6 h exposure (RT-PCR).	Safronova et al. (2003)
IL-8 and MCP-1	Human FLSs Human RAFLSs	+ +	↑ ↑	200 µM	Primary FLS collected from healthy donors. RAFLS collected from patients with rheumatoid arthritis. ↑ IL-8 and MCP-1 protein levels after 24 h exposure of FSL and RAFSL (ELISA) (FLS > RAFLS).	Zhao et al. (2015a)

Table S4.16 (continued)

End-point	Tissue, cell type or line	Results[a] (without metabolic activation)	Direction of response	Exposure concentration(s)	Comments	Reference
IL-8, IL-1α, and CCL-20	Human macrophage cell line derived from acute monocytic leukaemia (MonoMac 6)	+	↑	0.75 mM	↑ IL-8 protein levels after 16 h exposure (ELISA). ↑ IL-8, IL-1α, and CCL-20 mRNA expression levels after 4 (IL-1α and CCL-20 only) and 16 h exposure (qRT-PCR).	Lawrence et al. (2016)
IL-8 and MCP-1	Human osteoblasts	+	↑	10 ppm	Primary cells. ↑ IL-8 and MCP-1 protein levels after 12 and 24 h exposure (ELISA). ↑ mRNA expression levels after 4 h exposure (RT-PCR).	Queally et al. (2009)
IL-6, IL-8, and PGE2	Human 3D epithelial tissue culture model with TR146 cells	+	↑	> 0.5 and > 10 mmol/L	TR146 cells isolated from a squamous cell carcinoma of the buccal mucosa. ↑ IL-6 and IL-8 protein levels after 24 h exposure (< 10 mmol/L and > 0.5 mmol/L). ↑ PGE2 protein levels after 24 h exposure (> 10 mmol/L) (ELISA).	Schmalz et al. (2000)
ICAM-1, VCAM-1, and ELAM-1	HUVECs	+	↑	2 mM	↑ ICAM-1, VCAM-1, and ELAM-1 surface expression levels after 5 h exposure (FACS).	Goebeler et al. (1993)
IL-8, MCP-1, ICAM-1, and lymphocyte adhesion	HUVECs	+	↑	1, 2, and 4 mM	↑ IL-8 (2.0 and 4.0 mM) and MCP-1 (2.0 mM) protein levels after 8 h exposure. Cells exposed to 1 mM for 30 h secreted IL-8 (6 h peak) and MCP-1 (12 h peak) (ELISA). ↑ ICAM-1 expression levels increased after 6, 12, 24, and 48 h (WB) and 48 h (IHC) exposure to 1 mM. ↑ Lymphocyte adhesion after 3 h exposure to 1 mM.	Ninomiya et al. (2013)
TLR-4, TNFα, IL-1β, HLA-DR, and ICAM-1	Human myoblasts	+	↑	50 and 250 μM	Primary cells collected from healthy donors. ↑ TNFα and IL-1β protein levels after 24 and 48 h exposure. ↑ ICAM-1 surface expression after 48 h exposure (no significant effect on HLA-DR). ↑ TLR-4 expression after 48 h exposure to 50 and 250 μM (FACS).	Laumonier et al. (2020)

Table S4.16 (continued)

End-point	Tissue, cell type or line	Results[a] (without metabolic activation)	Direction of response	Exposure concentration(s)	Comments	Reference
IL-6, CXCL8, and CCL2	Human keratinocyte cell line HaCaT	+	↑ and ↓	500 and 1000 µM	↑ IL-6 protein levels after 24 and 48 h exposure (1000 µM) and ↓ CCL2 (500 and 1000 µM) (multiplex assay). ↑ IL-6 and CXCL8 mRNA expression levels and ↓ CCL2 (500 and 1000 µM) (qRT-PCR).	Klasson et al. (2021a)
IL-1β, IL-18, and NLRP3	Human keratinocyte cell line HaCaT	+	↑	0.5 and 1 mM	↑ IL-1β and IL-18 protein levels (1 mM) (multiplex). ↑ IL-1β and IL-18 mRNA expression levels (0.5 and 1 mM). ↑ NLRP3 inflammasome mRNA (1 mM) (qRT-PCR).	Klasson et al. (2021b)
IL-1β, IL-6, and TNFα	Human retinal pigment cell line ARPE-19	+	↑	600 µM	↑ IL-1β, IL-6, and TNFα mRNA expression levels after 12 h exposure (qRT-PCR).	Gu et al. (2021)
IL-8	Human microvascular endothelial cell line HMEC-1	–	NA	250 µM	No significant effect on IL-8 protein levels after 24 h exposure (ELISA)	Loboda et al. (2005)
IL-18	RhE	+	↑	48 mM	RhE generated from neonatal foreskin keratinocytes of healthy donors. ↑ IL-18 protein levels after 24 h exposure (ELISA).	Gibbs et al. (2018)
IL-8	NHEKs	–	NA	0.5 mM	↑ IL-8 protein levels after 16 h exposure of the FTSE model. No significant effect on NHEKs, RhEs, or BJ-terts (ELISA).	Frings et al. (2019)
	hDFs	–	NA			
	RhE	–	NA			
	BJ-terts	–	NA			
	Full-thickness skin equivalent (hDFs + NHEKs)	+	↑			
MCP-1 and IL-8	Human kidney cell line HK-2	+	↑	10 ppm	Primary neutrophils and monocytes collected from healthy donors. ↑ MCP-1 and IL-8 protein levels after 24 and 48 h exposure of HK-2, AGS, T84, and SAE cells, and after 12 and 24 h exposure of neutrophils. ↑ IL-8 protein levels after 12, 24, and 48 h exposure of monocytes. No significant effects on A549 cells (ELISA).	Devitt et al. (2010)
	Human gastric epithelium cell line AGS	+	↑			
	Human colonic carcinoma cell line T84	+	↑			
	Human SAE cells	+	↑			
	Human neutrophils	+	↑			
	Human monocytes	+	↑			
	Human alveolar epithelial cell line A459	–	NA			

Table S4.16 (continued)

End-point	Tissue, cell type or line	Results[a] (without metabolic activation)	Direction of response	Exposure concentration(s)	Comments	Reference
IL-1β, IL-6, TNFα, CD80, CD86, HLA-DR, and ICAM-1	Human monocyte cell line THP-1	+	↑	0.01 and 0.1 mM	PBMCs collected from healthy donors. ↑ IL-1β protein levels after 24 h exposure of THP-1 cells to 0.01 and 0.1 mM. No significant effect on TNFα (multiplex assay). ↑ CD86 and ICAM-1 surface expression, but not CD80 and HLA-DR, after 48 h exposure to 0.1 mM (FACS). ↑ IL-1β, TNFα, and IL-6 protein levels after 48 h exposure of monocytes to 0.1 mM (multiplex assay). ↑ CD86 and ICAM-1 surface expression, but not CD80, after 48 h exposure to 0.1 mM (FACS).	Caicedo et al. (2010)
	Human primary monocytes isolated from PBMCs	+	↑			
TNFα	Human monocytic cell line (U937)	+	↑	10 ppm	↑ TNFα mRNA expression levels after 24 h exposure (RT-PCR).	Luo et al. (2005)
Cobalt(III) chloride ($CoCl_3$)						
IL-1β, IL-6, TNFα, and TGF-β1	Human blood monocytes/macrophages	–	NA	100 ng/mL	PBMCs collected from healthy blood donors. No significant effects on IL-1β, IL-6, TNFα, and TGF-β1 protein levels after 24 h exposure in the absence of lipopolysaccharide stimulation (ELISA). [The Working Group noted that cobalt(III) chloride has a valence of III and, as such, is unstable/elusive. It is more likely to be the cobalt(II) chloride form.]	Wang et al. (1996b)
	Human monocytic cell line U937	–	NA			
IL-8	Human immature monocyte-derived dendritic MoDC cells	+	↑	125–750 µM	Primary monocytes collected from healthy blood donors. ↑ IL-8 protein levels after 24 h exposure (ELISA). Statistics reported only for the 500 µM dose.	Rachmawati et al. (2013)
IL-8 and CXCL10	Human macrophage cell line derived from acute monocytic leukaemia (MonoMac 6)	+	↑	0.5 mM	↑ IL-8 and CXCL10 protein levels after 24 h exposure (ELISA). ↑ mRNA expression levels after 4 h exposure (qRT-PCR).	Lawrence et al. (2014)

Table S4.16 (continued)

End-point	Tissue, cell type or line	Results[a] (without metabolic activation)	Direction of response	Exposure concentration(s)	Comments	Reference
IL-8, IL-13, TNFα, and IL-1β	Human keratinocyte cell line HaCaT	+	↑	10–1000 µg/mL	↑ IL-8 protein levels after 24 h exposure of HaCaT cells (IC_{20}, 117.5 µg/mL). ↑ IL-8, IL-13, and IL-1β protein levels (TNFα decreased) after 24 h exposure of THP-1 cells (128.7 µg/mL). ↑ IL-1β, IL-13, and IL-8 protein levels (↓ IL-6 and TNFα) after 24 h exposure of co-cultures (101.5 µg/mL) (multiplex assay).	Karri et al. (2021)
	Human monocytic cell line THP-1	+	↑ and ↓			
	Co-culture	+	↑ and ↓			
IL-8, IL-6, and ICAM-1	Human microvascular endothelial cell line HMEC-1	+	↑	0.25 and 0.5 mM	↑ IL-8 and IL-6 protein levels after 24 h exposure of HMEC-1 cells. ↑ sICAM-1 protein levels after 24 h exposure of HMEC-1 (0.5 mM) and MonoMac 6 cells (ELISA).	Anjum et al. (2016)
	Human macrophage cell line derived from acute monocytic leukaemia (MonoMac 6)	+	↑			
IL-1β, CCR7, TNFα, CD206, and IL-10	Human monocytic cell line THP-1	+	↑ and ↓	1, 10, and 100 µM	↓ IL-1β, CCR7, and IL-10 mRNA expression levels after 24 h exposure (1, 10, and 100 µM), and ↑ TNFα and CD206 (qRT-PCR).	Díez-Tercero et al. (2021)
IL-6, IL-8, TNFα, MIP-1a, IP-10, and MCP-1	Human primary synovial fibroblasts	+	↑	0.5 mM	Synovial fibroblasts collected from prosthetic-naive patients with osteoarthritis. ↑ Cytokine/chemokine protein levels after 24 h exposure included IL-6, IL-8, TNFα, MIP-1a, IP-10, and MCP-1 (multiplex assay).	Eltit et al. (2021)
Cobalt(II) sulfate ($CoSO_4$)						
IL-1β and TNFα	Human PBMCs	–	NA	50 and 100 µM	PBMCs collected from healthy blood donors. No significant ↑ in IL-1β protein levels after 48 h exposure or TNFα after 24 h exposure (50 and 100 µM) (ELISA). No significant ↑ in TNFα mRNA expression levels after 3 h exposure (100 µM) (RT-PCR).	Wellinghausen et al. (1996)

Table S4.16 (continued)

End-point	Tissue, cell type or line	Results[a] (without metabolic activation)	Direction of response	Exposure concentration(s)	Comments	Reference
Cobalt(II) nitrate ($Co(NO_3)_2$)						
TNFα and PGE2	Human leukocytes	+	↑	0.1, 1, and 10 ppm (1.7×10^{-9}, 1.7×10^{-8}, and 1.7×10^{-9} M)	Primary cells collected from healthy blood donors. ↑ TNFα protein levels after exposure (0.1, 1, and 10 ppm) for 1 and 3 h, and 1, 3, and 7 days. ↑ IL-6 protein levels after exposure (1 ppm) for 7 days and after exposure (10 ppm) for 3 h and 1 day. ↑ PGE2 protein levels after exposure (1 ppm) for 7 days and after exposure (10 ppm) for 1 h to 7 days (ELISA).	Liu et al. (1999)
Cobalt metal or cobalt-based NPs						
IFNγ, TNFα, IL-10, IL-4, IL-2, and IL-6	Human PBMCs	+	↓ and ↑	10^{-5}, 10^{-6}, and 10^{-7} mol/L	Cobalt metal NPs (< 50 nm), cobalt metal (< 2 µm), and $CoCl_2$. Cobalt metal induced ↓ release of IFNγ, TNFα, IL-10, IL-4, and IL-2 at all concentrations tested, and IL-6 at 10^{-7} mol/L. Cobalt metal NPs ↓ production of IL-2 and IL-10 at all concentrations tested and stimulated the release of TNFα at 10^{-6} and 10^{-7} mol/L and IFNγ at 10^{-7} mol/L. $CoCl_2$ ↓ production of IL-10, IL-2, and TNFα at 10^{-5} mol/L (multiplex assay).	Petrarca et al. (2006)
IL-8, MCP-1, and ICAM-1	HDMVECs	+	↑	1.0 mM ($CoCl_2$) 50 µg/mL (cobalt metal NPs)	Cobalt metal NPs (mean size, 28 nm) and $CoCl_2$. ↑ IL-8, MCP-1, and ICAM-1 protein levels after 24 h exposure to cobalt metal NPs and $CoCl_2$ (ELISA).	Peters et al. (2007)

Table S4.16 (continued)

End-point	Tissue, cell type or line	Results[a] (without metabolic activation)	Direction of response	Exposure concentration(s)	Comments	Reference
TNFα, IL-1β, and COX-2	Human monocytic cell line U937	+	↑	50–350 µM ($CoCl_2·6H_2O$) 5–50 µg/mL (cobalt metal NPs)	Cobalt metal NPs (mean size, 28 nm) and $CoCl_2·6H_2O$. ↑ TNFα protein levels after 10, 12, and 24 h exposure to 100 µM $CoCl_2$ and 10 µg/mL cobalt metal NPs, and ↑ IL-1β after 12 and 24 h exposure (cobalt metal NPs only) (ELISA). ↑ TNFα and IL-1β mRNA expression levels after 24 h exposure to 100 µM ($CoCl_2$) and 10 µg/mL (cobalt metal NPs), and COX-2 after 2, 3, and 24 h exposure (qRT-PCR).	Nyga et al. (2015)
IL-6 and TNFα	Primary monocytes/ macrophages isolated from PBMCs	+	↑	10 and 50 µg/mL	Cobalt metal (mean diameter, 2.5 ± 0.45 µm) PBMCs collected from healthy donors. ↑ IL-6 and TNFα protein levels after 72 and 144 h exposure (ELISA). ↑ IL-6 and TNFα mRNA expression levels after 144 h exposure (qRT-PCR).	Chen et al. (2017a)
IL-8 and TNFα	Human bronchial epithelial cell line BEAS-2B Human alveolar epithelial cell line A549	+ –	↑ NA	1–40 µg/mL	Co_3O_4 NPs (mean diameter, 22.1 ± 7.2 nm) BEAS-2B cells secrete IL-8 after 24 h exposure (20 µg/mL) and TNFα after 2 h exposure (1 µg/mL), but not IL-6. No significant effects on A549 cells (ELISA).	Cavallo et al. (2015)
ICAM-1, VCAM-1, E-selectin, MCP-1, and IL-8	HAECs HUVECs	+ +	↑ ↑	20 µg/mL	Co_3O_4 NPs (mean size, 17 ± 0.36 nm) ↑ MCP-1 and IL-8 protein levels after 24 h exposure of HAECs and HUVECs. Dose NR (ELISA). ICAM-1 and VCAM-1 mRNA expression levels peaked after 8 h exposure of HAECs, and E-selectin after 4 h exposure. ICAM-1, VCAM-1, and E-selectin mRNA expression levels peaked after 4 h exposure of HUVECs (RT-PCR).	Alinovi et al. (2015)

Table S4.16 (continued)

End-point	Tissue, cell type or line	Results[a] (without metabolic activation)	Direction of response	Exposure concentration(s)	Comments	Reference
NLRP3, IL-1β, and IL-18	Human fetal hepatocytic L02 cells	+	↑	5, 7.5, and 10 µg/mL	Cobalt metal NPs (mean diameter, 20 nm). ↑ IL-18 and IL-1β protein levels after 24 h exposure (7.5 and 10 µg/mL) (ELISA). ↑ NLRP3 inflammasome protein levels after 24 h exposure (5, 7.5, and 10 µg/mL), and IL-1β (7.5 µg/mL) (WB).	Feng et al. (2020)
TNFα and PDGF-BB	Primary mononuclear cells	–	NA	0.05 mg/mL	Cobalt metal NPs (mean size, 28 nm). Mononuclear cells collected from healthy donor blood. Cobalt metal NPs preconditioned with platelet-rich human plasma for 30 min and then incubated with mononuclear cells for 20 h. No significant increase in TNFα or PDGF-BB after 20 h exposure (ELISA).	Guildford et al. (2009)

3D, three-dimensional; BJ-terts, telomerase-immortalized normal human fibroblasts; CCL2/-20, C-C motif chemokine ligand 2/20; CCR7, C-C chemokine receptor type 7; CD80/86/206, cluster of differentiation 80/86/206; COX-2, cyclooxygenase-2; CXCL8/10, chemokine (C-X-C) motif ligand 8; ELAM-1, endothelial leukocyte adhesion molecule-1; ELISA, enzyme-linked immunosorbent assay; FACS, fluorescence-activated cell sorting; FLS, fibroblast-like synoviocytes; FTSE, full-thickness skin equivalent; HAEC, human aortic endothelial cell; HBEC, human brain endothelial cell; hDF, human dermal fibroblast; HDMVEC, human dermal microvascular endothelial cell; HLA-DR, human leukocyte antigen DR; HPAEC, human pulmonary aortic endothelial cell; HPMVEC, human pulmonary microvascular endothelial cell; HUVEC, human umbilical vein endothelial cell; IC_{20}, 20% inhibitory concentration; ICAM-1, intercellular adhesion molecule-1; IFNγ, interferon gamma; IHC, immunohistochemistry; IL, interleukin; IP-10, interferon gamma-produced protein 10; MCP-1, monocyte chemoattractant protein-1; MIP-1a, macrophage inflammatory protein-1a; mRNA, messenger RNA; NA, not applicable; NHEK, normal human epithelial keratinocyte; NLRP3, NOD-like receptor protein 3; NP, nanoparticle; NR, not reported; P, particle; PBMC, peripheral blood mononuclear cell; PDGF-BB, platelet-derived growth factor-BB; PGE2, prostaglandin E2; ppm, parts per million; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RAFLS, rheumatoid arthritis fibroblast-like synoviocytes; RASF, rheumatoid arthritis synovial fibroblasts; RhE, reconstructed human epidermis; RT-PCR, real-time polymerase chain reaction; SAE, small airway epithelial; sICAM-1, soluble ICAM-1, intercellular adhesion molecule-1; TGF-β1, transforming growth factor-β1; TLR-4, Toll-like receptor-4; TNFα, tumour necrosis factor alpha; VCAM1, vascular cell adhesion molecule-1; WB, western blot.

[a] +, positive; –, negative; ↓, decrease(d); ↑, increase(d).

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