Supplementary Table 1 Environmental safety evaluation of ENMs after acute exposure in *C. elegans*

ENMs (size)	Dose	Duration	Adverse effects	Ref
CeO_2-NPs (8.5 nm)	1-100 nM	L1-larvae to adult	Decreased lifespan, increased intestinal lipofuscin accumulation, increased oxidative damage.	[1]
CeO_2-NPs (15, 30, 45 nm)		24-hr	Altered expression of *hsp-16.1*, *hsp-16.2*, *gst-4*, and *cyp35a2*, decreased egg number.	[2]
CeO_2-NPs (15 and 45 nm)		24-hr	Increased expression of *cyp35a2*, and decrease in fertility, and survival.	[3]
ZnO-NPs (1.5 nm)	325-1625 mg/L	4, 24, 72-hr	Increased lethality and P*mtl-2::gfp* expression, and decreased brood size and movement.	[4]
ZnO-NPs (20 nm)	0.4-8.1 mg/L	24-hr, 5-day	Increased lethality, suppressed reproduction and growth.	[5]
ZnO-NPs (25 and 100 nm)			LC_{50} was 0.32 mg/L or 2 mg/L (25 nm or 100 nm)	[6]
TiO_2-NPs (7 and 20 nm)		24-hr	Increased expression of *cyp35a2*, and decrease in fertility, and survival.	[3]
TiO_2-NPs (50 nm)	24-239.6 mg/L	24-hr, 5-day	Increased lethality, suppressed reproduction and growth.	[5]
TiO_2-NPs (4, 10, 60, 90 nm)	0.001-10 μg/L	L1-larvae to day-1 adult	Decreased survival, growth, reproduction, locomotion behavior, and metabolism, and increased intestinal autofluorescence and ROS production.	[7]
TiO_2-NPs (25 and 100 nm)			LC_{50} was 77 mg/L (25 nm)	[6]
Al_2O_3-NPs (60 nm)	10.2-407.8 mg/L	24-hr, 5-day	Increased lethality, suppressed reproduction and growth.	[5]
Al_2O_3-NPs (60 nm)	6.3–203.9 mg/L	24-hr, L1 larvae-adult.	Increases in lethality, stress response, and intestinal lipofuscin autofluorescence.	[8]
Al_2O_3-NPs (60 nm)	0.1-50000 μg/L	6 and 12-hr, L1-larvae to adult	Decreased locomotion behavior.	[9]
Ag-NPs (14-20 nm)	0.05-0.5 mg/L	24, 72-hr	Altered gene expression profile, and suppressed reproduction.	[10]

CIT-Ag-NPs (7 nm), PVP-Ag-NPs (21 nm), PVP-Ag-NPs (75 nm)	0.5-50 mg/L	24-hr	Growth inhibition.	[11]
Ag-NPs (20 nm)	0.05-0.5 mg/L	4, 24-hr	Increase in ROS formation, altered gene expression, and reduced reproduction.	[12]
Ag-NPs (1 nm), PVP-coated Ag-NPs (28 nm)	0.5-10 mg/L or 0.6-3 mg/L	24, 48, 72-hr	Increased lethality.	[13]
Citrated coated Ag-NPs (50.6 nm)	1-1000 mg/L	24, 48-hr	Decreased survival and reproduction.	[14]
CuO-NPs (<50 nm)	1-50 μg/mL	24-hr	Altered gene expression patterns.	[15]
DMSA-coated Fe_2O_3-NPs (9 nm)	0.001-100 mg/L	24-hr, L1-larvae to day-1 adult	Decreased survival, growth, reproduction, locomotion behavior, and metabolism, and increased intestinal autofluorescence and ROS production.	[16]
hydroxylated fullerene (4.7 and 40.1 nm)	1-100 μg/mL		Decreased survival ratio, shortened lifespan, and reduced reproduction rate and body size.	[17]
$NaYF_4$:Yb,Er	1-5 mg/mL	3, 24-hr	Reduced survival.	[18]
MSA-capped CdSe/ZnS	0.01-1 μM	3 days	Increased embryo mortality, defect in egg-laying, and reduced lifespan.	[19]
Citrate-coated Au-NPs	5.9 mg/L	4 nm	Different expression of 797 genes.	[20]

Supplementary Table 2 Environmental safety evaluation of ENMs after chronic exposure in *C. elegans*

ENMs (size)	Dose	Duration	Adverse effects	Ref
Silica-NPs (60 nm)	0.25-50 mg.mL	The full generation from day-1 adult	Reproductive senescence.	[11]
Al_2O_3-NPs (60 nm)	8.1-30.6 mg/L	10-days	Increase of intestinal autofluorescence, and formation of stress response and oxidative damage.	[21]
Al_2O_3-NPs (60 nm)	0.005-23.1 mg/L	10 days	Decreased locomotion behavior, and increased stress response and oxidative stress.	[22]
DMSA coated Fe_2O_3-NPs (9 nm)	1-5000 µg/L	L1-larvae to day-8 adult	Decreased survival, growth, reproduction, locomotion behavior, and metabolism, and increased intestinal autofluorescence and ROS production.	[16]
MPA-CdSe QDs (5-6 nm)	20 nM	16 days	Difficulty in egg laying, damaged egg left in the vulva and egg without an intact egg shell, and decreased growth, brood size and lifespan.	[23]

Supplementary Table 3 Comparative analysis of *C. elegans* based toxicities of TiO_2-NPs with those in other *in vitro* and *in vivo* assay systems

Organism	Size	Toxicity array used	Dose	Duration	Adverse effects	Ref.
Human pulmonary epithelial, cervical cancer, hepatocarcinoma, and monocytic leukemia cells	25 nm	Cytotoxicity and gene expression	75 mg/L	6 hr	Cell viability and induce expression of stress-related genes	[24]
Human skin keratinocytes	25 and 100 nm	Lipid and protein peroxidation	50 mg/L,	4 hr	Photocytotoxicity, cell membrane damage	[25]
Human embryonic kidney cell	25 nm	Oxidative stress and apoptosis	50 mg/L	24, 48 and 72 hr	Oxidative stress and apoptosis	[26]
Human hepatocarcinoma, lung epithelial, and monocytic leukemia cells	21 nm	Metabolic activation and cell death	10 mg/L	24, 48, 72 hr	Decreased metabolic activation, and increased cell death	[27]
Human hepatoblastoma cells	7 and 10 nm	Total glutathione, DCFH-DA, DNA strand breaks	10 mg/L	4 hr	DNA damage	[28]
Human keratinocytes cells	20 nm	Micronucleus, mitochondrial DNA damage, ROS	5 mg/L	24, 48, 72 hr	Cytotoxic and genotoxic	[29]
Murine fibroblast and pre-osteoblast cells	25 nm	Morphology, LDH assay, IL-6 and TNF-β assay, DNA fragmented	10 mg/L	2, 24, 48 hr	Cellular toxicity and inflammation	[30]
Murine pre-osteoblasts cells	5 and 32 nm	Cell viability, LDH assay, apoptosis, mitochondrial membrane permeability, gene expression	5 mg/L	24, 48, and 72 hr	Cytotoxicity	[31]
Murine microglia cells		Morphology, chromosome condensation, cell cycle	16 mg/L	24 hr	Apoptosis	[32]
Human	3.2 nm	Live viability, LDH assay,	100	50 hr	Cytotoxicity and	[33]

dermal fibroblast and lung epithelial cells		mitochondrial activity, IL-8 expression	mg/L		inflammatory response	
Human lymphocyte	100 nm	Comet assay, DNA laddering assay	0.25 mM	3 hr	Mitochondrial damage, genotoxic	[34]
Rat adrenal medulla pheochromocytoma	21 nm	Viability, ROS	10 mg/L	6, 12, 24 and 48 hr	Apoptosis	[35]
Non-small cell lung cancer cells	11-150 nm	Cell viability, necrosis and apoptosis, LDH assay	50 mg/L	1 hr	Cytotoxicity	[36]
Human monoblastoid cells	100 nm	Membrane permeability, DNA quantification	0.005 g/L	24 and 48 hr	Apoptotic and necrotic modifications	[37]
Human keratinocytes cells	25 nm	Lipid peroxidation, cell proliferation	10 mg/L	4 hr	Perturbs the cytoskeleton architecture, and inhibit cell growth	[38]
Bottlenose dolphin leukocytes	25 nm	Comet assay, cytotoxicity	50 mg/L	4, 24,48 hr	Genotoxic	[39]
Human keratinocytes cells	25 and 100 nm	ROS, cell toxicity	200 mg/L	4 hr	Mitochondria disruption	[40]
Mouse fibroblast cells	100 nm	ROS, SOD, LDH, GSH, survival, cell morphology	60 mg/L	24 and 48 hr	Cell morphology changed, apoptosis	[41]
Mice	100 nm	Pathological examination, monoamine neurotransmitter levels	500 µg/ mice	30 day	Lesions on murine brain	[42]
Mice	33 nm	Comet assay, karyological assay	40 mg/kg	7 day	Genotoxicity	[43]
Mice	8 and 10.4 nm	Cells and total protein, TNF-α and IL-6 expression	5 µg/mice	24 hr and 30 day	Inflammation	[44]
Apolipoprotein E knockout (ApoE-/-) mice	12 and 21.6 nm	Plaque progression in aorta, vasodilatory function, gene expression levels	0.5 mg/kg	4 weeks	Increase in plaque progression in aorta	[45]
Mice	25 nm	Cytoplasmic aconitase, L-lactate dehydrogenase A chain, carbonic anhydrase 1, pyruvate kinase isoform M2	2.5 mg/mice	7 day	Induced toxicities evaluated at the protein level	[46]

		and peroxiredoxin 6, expression of heat shock protein, moesin and apolipoprotein A-1 precursor				
Mice	5-6 nm	Nephric inflammation, cell necrosis and dysfunction. expression of nucleic factor-涣B, tumor necrosis factor-α, macrophage migration inhibitory factor, interleukin-2, interleukin-4, interleukin-6, interleukin-8, interleukin-10, interleukin 18, interleukin-1β, cross-reaction protein, transforming growth factor-菖, interferon-幼 and CYP1A1, and heat shock protein 70	2.5 mg/kg	90 day	Nephric injury	[47]
Mice	6.9 nm	Histopathological and biochemical analysis including ROS, lipid peroxidation, antioxidant enzyme activity, glutathione, and ascorbic acid	5 mg/kg	14 day	Nephrotoxicity, oxidative stress	[48]
Mice	21 nm	Maternal lung inflammation, gestational and litter parameters, offspring neurofunction, and fertility	42 mg/m^3	8-18 day	Lung inflammation, offspring neurobehavioral alterations	[49]
Mice	5 nm	Expressions of inflammatory cytokines, histopathological changes, and hepatocytes apoptosis	5-150 mg/kg	14 day	Inflammatory responses, and liver injury	[50]
Mice	5 nm	Organs and serum biochemical parameters	5 mg/kg	14 day	Toxicity formed in liver	[51]
Mice	80-110 nm	Histopathology, passive behavior, loss of appetite, tremor, and lethargy	324 mg/kg	24 and 48 hr, 7 and 14 days	Hhepatocellular necrosis and apoptosis, hepatic fibrosis, renal glomerulus swelling and interstitial pneumonia	[52]
Mice	15, 50 and 100 nm	Expression of LPS, IL-1β, MCP-1, and KC	8mg/kg	24 hr	Lung inflammation	[53]
Mice	5 nm	Norepinephrine, dopamine,	5	60 day	Impaired spatial	[54]

		dihydroxyphenylacetic acid, 5-hydroxytryptamine, acetylcholine, glutamate, and NO	mg/kg		recognition memory ability	
Rat	21 nm	LC50, microvascular oxidative stress, NO	5 μg/rat	24 hr	Microvascular dysfunction	[55]
Rat	13. and 42 nm	GSH, SOD, H_2O_2, TNF-α, and IL-1β	0.2 mg/kg	7 day	Oxidative damage, synovium hypotrophy and lymphocytes and plasma cells infiltration	[56]
Rat	5 nm	LDH, 8-isoprostane	2 mg/m^3	6 hr	Inflammatory response	[57]
Rat	25 nm	Input/output (I/O) functions, pairedpulse reaction (PPR), field excitatory postsynaptic potential, population spike amplitude	100 mg/kg	2 and 21 days	Neurotoxicity	[58]
Larval zebrafish	25-70 nm	Hatch ability, survival, malformation, moving velocity and activity	0.1 mg/L	5 day	Behavioral toxicity	[59]
Zebrafish	30 nm	SOD, CAT, GSH, MDA, .OH	50 mg/L	7 day	Oxidative damage	[60]
Trout erythrocyte	10-150 nm	Hemolysis rate, NADH, comet assay	1.6 mg/L	10 and 60 min	DNA damage,	[61]
D. magna	21 nm	Survival	0.25 mM,	96 hr, 21 day	Mortality	[62]
D. magna	100 nm	Molting	0.73 mg/L	24, 48, 72, 96 hr	Molting inhibition	[63]
E. fetida	14-16 nm	Expression of metallothionein and superoxide dismutase, induction of apoptotic activity, phagocytosis	0.1 mg/L	24 hr	Altered antioxidant system	[64]
E. fetida	10-20 nm	Antioxidant enzymes, DNA damage, cellulase activity, mitochondria damage	1.0 g/kg dry soil	7 day	Mitochondrial damages, DNA damage	[65]
Porcellio scaber	15 nm	CAT and GST	0.5 μg/g food	3 days	Decreased antioxidant enzymes	[66]
Lumbricus terrestris	100-300 nm	Intestinal epithelium and chloragogenous	10 mg/kg soil	7 days	Apoptosis	[67]
C. elegans	30 nm	lethality, growth,	0.05-5	L1-larvae	decreased survival,	[68]

		reproduction, locomotion behavior, ROS production	0 µg/L	to day-1 adult	growth, reproduction, locomotion behavior, and increased ROS production	
C. elegans				24-hr	Increased expression of *cyp35a2*, and decrease in fertility, and survival.	[3]
C. elegans	50 nm	lethality, reproduction and growth	24-23 9.6 mg/L	24-hr, 5-day	Increased lethality, suppressed reproduction and growth.	[5]
C. elegans	4, 10, 60, 90 nm	survival, growth, reproduction, locomotion behavior, metabolism, intestinal autofluorescence, and ROS production.	0.001-10 µg/L	L1-larvae to day-1 adult	Decreased survival, growth, reproduction, locomotion behavior, and metabolism, and increased intestinal autofluorescence and ROS production.	[7]
C. elegans	25 and 100 nm	survival			LC_{50} was 77 mg/L (25 nm)	[76]

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