Supplementary material for

Mechanisms of toxic action of Ag, ZnO and CuO nanoparticles to selected ecotoxicological test organisms and mammalian cells *in vitro*: a comparative review.

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Figure SI. Schematic representation of the scope of the current review.

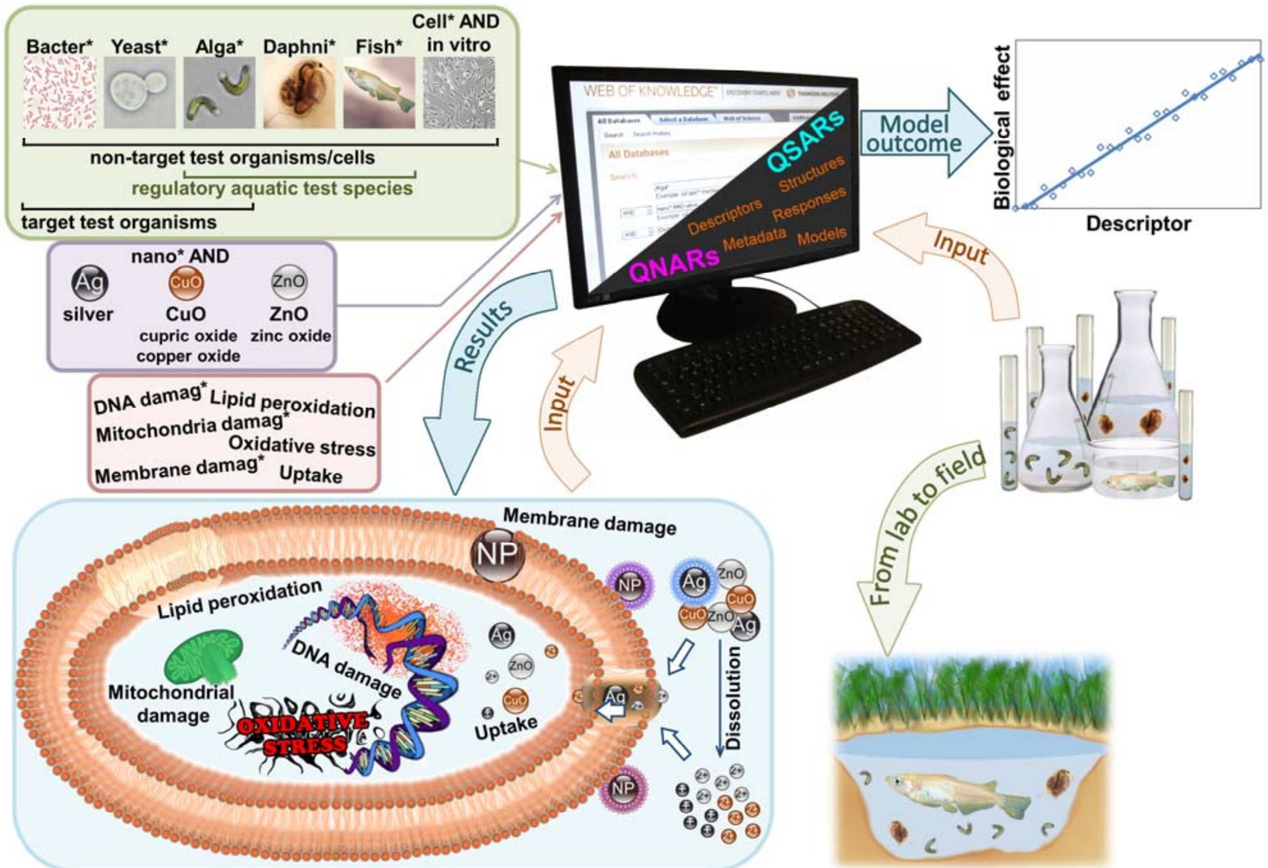

Table SI Number of papers in ISI WoS (May 5th and 6th, 2013) concerning Ag, ZnO or CuO NPs and different test organisms or cells. The search terms for different nanoparticles were as follows: Topic=(nano* AND silver); Topic=(nano* AND ZnO OR Zinc oxide); Topic=(nano* AND CuO OR cupric oxide OR copper oxide). These search terms were refined with different terms for test organisms indicated. In bold are designated the organisms groups that were further addressed for retrieving information on toxicity mechanisms. The % values in the brackets are calculated for selected organisms (in bold).

		Ag NPs *nano* AND silver*	ZnO NPs *nano* AND ZnO OR Zinc oxide*	CuO NPs *nano* AND CuO OR cupric oxide OR copper* oxide
		31 558	**47 714**	**30 409**
	Additional search terms:			
1	**bacter***	**2108 (69%)**	**745 (46%)**	**487 (52%)**
2	MRSA	45	3	3
3	Escherichia	1501	438	250
4	**yeast***	**119 (3.9%)**	**66 (4.1%)**	**49 (5.3%)**
5	**alga***	**84 (2.7%)**	**103 (6.3%)**	**65 (7.0%)**
6	protozoa*	11	9	9
7	ciliate*	6	5	4
8	**daphni***	**68 (2.2%)**	**78 (4.8%)**	**32 (3.4%)**
9	crustacea*	10	17	15
10	nematode*	17	20	39
11	C. elegans OR C.elegans	17	14	2
12	**fish***	**109 (3.6%)**	**99 (6.1%)**	**79 (8.5%)**
13	**cell* AND *in vitro***	**567 (19%)**	**532 (33%)**	**216 (23%)**
1-13	Total for all test organisms:	4662	2129	1250
	Total for selected organisms (in bold):	**3055 (100%)**	**1623 (100%)**	**928 (100%)**

Table SII Classification of Journals in which toxicity data for Ag, ZnO or CuO NPs and different test organisms or cells were published and that are cited in the current Review. Classification into categories is arbitrary and was introduced by authors. The number of papers for each journal cited in the current Review is given in the brackets. See also Table II in the main text.

Biotechnology journals (2 papers)

1. Appl Biochem Biotechnol (1)
2. Nat Biotech (1)

Chemistry journals (17 papers)

1. Acc Chem Res (2)
2. Anal Bioanal Chem (2)
3. Biochem Biophys Res Commun (1)
4. BioMetals (2)
5. Chem Soc Rev (1)
6. Comb Chem High T Scr (1)
7. JBIC J Biol Inorg Chem (1)
8. J Am Chem Soc (2)
9. Langmuir (4)
10. RSC Adv (1)

Ecotoxicology and Environmental Chemistry journals (52 papers)

1. Aquat Toxicol (2)
2. Chemosphere (5)
3. Ecotoxicol Environ Saf (1)
4. Environ Chem (1)
5. Environ Poll (5)
6. Environ Sci Technol (19)
7. Environ Sci Poll Res Intl (1)
8. Environ Sci Process Impact (1)
9. Environ Toxicol Chem (6)
10. J Environ Monit (1)
11. J Environ Sci Health Part A (1)
12. J Haz Mat (3)
13. Sci Tot Environ (4)
14. Soil Biol Biochem (1)
15. Water Res (2)
16. Ann Bot (1)

Interdisciplinary journals (7 papers)

1. Nature (1)
2. PLoS One (3)
3. Proc Nat Acad Sci (2)
4. Science (1)

Material Sciences journals (3 papers)

1. Adv Funct Mat (1)
2. Biomaterials (2)

Medical journals (13 papers)

1. Adv Drug Delivery Rev (1)
2. Am J Resp Crit Care Med (3)
3. Ann Ist Super Sanita (1)
4. Ann Rev Pharmacol Toxicol (1)
5. Apoptosis (2)
6. Curr Med Chem (1)
7. Cytometry A (1)
8. Free Radical Biol Med (1)
9. Iran Biomed J (2)

Microbiology journals (5 papers)

1. Appl Environ Microbiol (2)
2. Clin Microbiol Rev (1)
3. J Appl Microbiol (1)
4. Microbiol Res (1)

Nanotechnology journals (30 papers)

1. ACS Nano (9)
2. J Nanoparticle Res (3)
3. Nano Lett (4)
4. Nanoscale (3)
5. Nanoscale Res Letters (1)
6. Nanotechnology (2)
7. Nat Nano (2)
8. Small (5)
9. Wiley Interdiscip Rev Nanomed Nanobiotechnol (1)

Physics journals (1 paper)

1. Appl Phys Lett (1)

Toxicology journals (37 papers)

1. Arch Toxicol (4)
2. Chem Res Toxicol (5)
3. Comp Biochem Physiol C Toxicol Pharmacol (1)
4. Crit Rev Toxicol (1)
5. Food Chem Toxicol (1)
6. Nanotoxicology (8)
7. Part Fibre Toxicol (1)
8. Toxicol Sci (1)
9. Toxicol (2)
10. Toxicol in Vitro (8)
11. Toxicol Lett (3)
12. Toxicol Res (2)

Table SIII Number of papers on potential mechanisms of toxic action of Ag, ZnO and CuO nanoparticles for different test organisms/cells in ISI WoS on March 5th and 6th, 2013. For bibliometry, the primary search terms nano* AND silver, nano* AND ZnO OR Zinc oxide, nano* AND CuO OR cupric oxide OR copper oxide were further refined with different terms describing the test organisms and mechanisms as indicated.

	Bacter*	Yeast*	Alga*	Daphni*	Fish*	Cell* AND *in vitro*	Total for all organisms	%
	Ag NPs							
Additional search terms								
DNA damag*	15	2	0	3	6	62	88	16%
Lipid peroxidation	8	0	2	0	5	18	33	5,9%
Mitochondria* damag*	2	1	0	0	1	22	26	4,6%
Oxidative stress	35	0	8	9	22	131	205	36%
Membrane damag*	28	1	1	0	1	24	55	10%
Uptake	47	3	8	12	11	74	155	28%
Total	**135**	**7**	**19**	**24**	**46**	**331**	**562**	
(%, all organisms)	**(24%)**	**(1.2%)**	**(3.4%)**	**(4.3%)**	**(8.2%)**	**(59%)**	**(100%)**	**100%**
	ZnO NPs							
DNA damag*	11	2	1	1	4	49	68	13%
Lipid peroxidation	14	1	2	9	11	21	58	10,8%
Mitochondria* damag*	3	0	0	2	1	15	21	3,9%
Oxidative stress	38	7	8	23	19	143	238	44%
Membrane damag*	25	1	3	1	1	18	49	9%
Uptake	35	2	7	13	4	40	101	19%
Total	**126**	**13**	**21**	**49**	**40**	**286**	**535**	
(%, all organisms)	**(24%)**	**(2.4%)**	**(3.9%)**	**(9.2%)**	**(7.5%)**	**(53%)**	**(100%)**	**100%**
	CuO NPs							
DNA damag*	5	2	0	1	0	24	32	11%
Lipid peroxidation	5	1	1	7	5	29	48	16,8%
Mitochondria* damag*	0	0	0	1	0	8	9	3,2%
Oxidative stress	19	7	8	11	10	74	129	45%
Membrane damag*	5	1	2	1	1	6	16	6%
Uptake	21	2	10	3	1	14	51	18%
Total	**55**	**13**	**21**	**24**	**17**	**155**	**285**	**100%**
(%, all organisms)	**(19%)**	**(4.6%)**	**(7.4%)**	**(8.4%)**	**(6.0%)**	**(54%)**	**(100%)**	

Table SIV Highlights for molecular toxicity mechanisms of silver nanoparticles (Ag NP) in mammalian cell cultures. Numbers (e.g., Ag NP5) indicate the primary size of nanoparticles in nm. The information is summarized in Figure 3 in the main text.

	Highlights	References
Effect on cell viability (LDH, MTT, XTT assay)	Ag^+ and Ag NP were toxic in the following order: Ag NP5 > Ag^+ > Ag NP20 > Ag NP50 in A549, HepG2, MCF-7, SGC-7901 cell lines. Ag^+ and Ag NP were toxic in L929 fibroblasts in the following order Ag NP20 > Ag^+ > Ag NP80 > Ag NP113. In RAW 264.7 macrophages, Ag NP20 and Ag^+ had similar toxicity.	Hussain et al. 2005; Arora et al. 2008; Kim et al. 2009; Liu et al. 2010; Park et al. 2010; Nowrouzi et al. 2010; Foldbjerg et al. 2011; Park et al. 2011; Szmyd et al. 2013
Cellular uptake	Relatively higher total concentrations of Ag were present in HepG2 cells exposed to Ag NP5 than to Ag NP20 and Ag NP50.	Hussain et al. 2005; Kim et al. 2009; Liu et al. 2010; Nowrouzi et al. 2010; Park et al. 2010; Foldbjerg et al. 2011
Extracellular ROS	Extracellular ROS induced by Ag NP did not correlate with intracellular ROS in RAW 264.7 cells.	Park et al. 2011
Intracellular ROS:		
2',7'-H_2DCFDA, MitoSox Red	In RAW 264.7 macrophages Ag NP20 induced more ROS than Ag NP80 and Ag NP113. ROS was induced only near cytotoxic concentrations.	Hussain et al. 2005; Kim et al. 2009; Foldbjerg et al. 2011; Park et al. 2011
Depletion of glutathione (GSH)	In HepG2 cells only Ag NP5 and not Ag^+, Ag NP20 or Ag NP50 depleted GSH level.	Hussain et al. 2005; Arora et al. 2008; Liu et al. 2010; Park et al. 2010
Regulation of ROS-responsive genes	In HepG2 cells the genes of metallothionein 1b and glutathione peroxidase (GPx) were induced by Ag^+ and not Ag NP10.	Kim et al. 2009
Inhibition of ROS-quencing enzymes	Superoxide dismutase (SOD) activity decreased after exposure of HepG2 cells to Ag^+, Ag NP5 and Ag NP20 and not to Ag NP50.	Arora et al. 2008; Liu et al. 2010; Nowrouzi et al. 2010
DNA damage	DNA damage in HepG2 and A549 cells exposed to Ag^+ or Ag NP was prevented by pretreatment with antioxidant N-acetylcysteine. DNA damage in RAW 264.7 cells exposed to Ag NP5-113 was not significant and not the primary cause of the cell death.	Arora et al. 2008; Kim et al. 2009; Foldbjerg et al. 2011; Park et al. 2011; Szmyd et al. 2013
Changes in cell morphology	Ag^+ and Ag NP5 caused similar changes in HepG2 cells' morphology.	Hussain et al. 2005; Arora et al. 2008; Kim et al. 2009; Liu et al. 2010; Nowrouzi et al. 2010
Inflammation	Ag NP induced various inflammatory markers in RAW 264.7 macrophages in the following order: Ag NP20 > Ag NP80 > Ag NP113.	Park et al. 2010; Park et al. 2011; Bachand et al. 2012

	Ag NP20 and not Ag NP60 induced IL-8 in A549 cells at 0.35 µg/L.	
Cell cycle arrest	In HepG2 cells Ag NP and Ag^{+} caused cell cycle arrest in S phase the following order: Ag NP5 > Ag^{+} > Ag NP20 > Ag NP50.	Liu et al. 2010; Park et al. 2010
Apoptosis/ Necrosis	In HT-1080 and A431 cells apoptosis prevailed at low and necrosis at high concentrations of Ag NP. Less than 10% of HepG2cells were positive for early apoptosis after exposure to cytotoxic concentrations of Ag NP. Less than 20% of A549cells were positive for early apoptosis and about 50% cells were positive for necrosis after exposure to AG NP.	Arora et al. 2008; Liu et al. 2010; Nowrouzi et al. 2010; Foldbjerg et al. 2011; Szmyd et al. 2013

Table SV Highlights for molecular toxicity mechanisms of copper oxide nanoparticles (nCuO) in mammalian cell cultures. The information is summarized in Figure 3 in the main text.

	Highlights	References
Effect on cell viability (LDH, MTT, XTT assay)	nCuO were among the most toxic NPs to A549 cells.Cu^{2+} was less toxic in A549 and HepG2cells than nCuO. Cu^{2+} contributed to less than 50% of the overall cytotoxicity from nCuO exposure in A549 cells. Cu^{2+} chelators D-penicillamine and desferoxamine failed to mitigate the cytotoxicity of nCuO in HEp-2 cells. Sonication of the nCuO increased the cytotoxicity in A549 cells.	Karlsson et al. 2008; Fahmy and Cormier 2009; Lanone et al. 2009; Ahamed et al. 2010; Cronholm et al. 2011; Cho et al. 2012; Perreault et al. 2012; Piret et al. 2012; Zhang et al. 2012; Wang et al. 2012
Cellular uptake	Preferential accumulation of Cu ions from nCuO was observed in sulphur-rich areas of HepG2 cells. CuO entered into the A549 cells through endocytosis. A fraction of nCuO was not excreted by A549 cells because of the deposition in the mitochondria and nucleus.	Cronholm et al. 2011; Piret et al. 2012; Wang et al. 2012
Intracellular ROS:		
2',7'-H_2DCFDA, MitoSox Red	Pretreatment with antioxidant N-acetylcysteine mitigated the cytotoxicity of nCuO in A549 cells (Cho et al., 2012).	Karlsson et al. 2008; Fahmy and Cormier 2009; Piret et al. 2012; Zhang et al. 2012; Wang et al. 2012
Depletion of GSH and lipid peroxidation	Depletion of reduced glutathione and induction of lipid peroxidation	Fahmy and Cormier 2009; Ahamed et al. 2010; Perreault et al. 2012
Regulation of ROS-quencing enzymes	CAT and GR activity decreased, GPx activity increased and SOD activity did not change after exposure of HEp-2 cells to 30 nm nCuO. SOD and CAT activity increased after exposure of A451 cells to 65 nm nCuO.	Fahmy and Cormier 2009; Ahamed et al. 2010
DNA damage	Increased levels of p53, Rad51 and MSH2 in A549 cells exposed to CuO. DNA fragmentation and micronucleus formation in Neuro-2A cells at low sub-toxic concentrations of nCuO.Oxidative DNA damage after 4-h exposure, temporal activation of p38 and p53 after 4-h exposure and irreversible DNA damage after 8-h exposure of nCuO to A549 cells. Low levels of DNA damage after 4-h exposure of nCuO to A549 cells.	Karlsson et al. 2008; Ahamed et al. 2010; Cronholm et al. 2011; Perreault et al. 2012; Wang et al. 2012
Changes in cell morphology	The number of A549 cells with nCuO particles attached to the cell surfaces was higher when cells were exposed to nCuO in serum-deficient medium compared to medium with serum. Accumulation of nCuO particles in A549 cells decreased lysosomal activity and caused the appearance of secondary	Cronholm et al. 2011; Wang et al. 2012

	lysosomes.	
Inflammation	Activation of IL-1, IL-8, AP-1, NF-źB, MIP-2 by both nCuO and nCuO supernatant in A549 cells. CuO but not CuO supernatant recruited eosinophils. Overexpression of IL-7, IL-8, IL-12A, IL-18, CSF-1, M-CSF in HepG2 exposed to nCuO. IL-8 overproduction in HepG2 exposed to CuO was abolished by treatment with antioxidant N-acetylcysteine. Increased DNA binding of Nrf2, NF-kB (transient) and AP-1 in HepG2 cells exposed to nCuO.	Cho et al. 2012; Piret et al. 2012; Zhang et al. 2012

CAT-catalase, GSH – reduced glutathione , GPx – glutathione peroxidase, GR-glutathione reductase, SOD-superoxide dismutase

Table SVI Highlights for molecular toxicity mechanisms of zinc oxide nanoparticles (nZnO) in mammalian cell cultures. The information is summarized in Figure 3 in the main text.

	Highlights	**References**
Effect on cell viability (LDH, MTT, XTT assay)	nZnO were among the most toxic NPs cells to A549, BEAS-2B and RAW 264.7 cells. Supernatant of nZnO had the same toxicity as nZnO in A549 cells. Zn^{2+} and 10-30 nm nZnO were more toxic than 100 nm nZnO in Ana-1 cells.	Karlsson et al. 2008; Xia et al. 2008; Kim et al. 2010; Song et al. 2010; Cho et al. 2012; Li et al. 2012; Sharma et al. 2012; Shi et al. 2012; Zhang et al. 2012; Guan et al. 2012
Cellular uptake	Undissolved nZnO nanoparticles enter caveolae in BEAS-2B but enter lysosomes in RAW 264.7 cells. nZnO was rapidly dissolved in the MCF-7 cells. Zn^{2+} from nZnO concentrated in the lysosomal compartments of RAW 264.7 cells.	Xia et al. 2008; Sharma et al. 2012; Shi et al. 2012
Extracellular ROS	ZnO induced extracellular H_2O_2 . Extracellular ROS did not correlate with intracellular ROS .	Xia et al. 2008; Song et al. 2010; Shi et al. 2012
Intracellular ROS: 2',7'-H_2DCFDA, MitoSox Red	nZnO induced oxidative DNA lessions but not H_2O_2 in A549 cells. nZnO induced mitochondrial O_2^- but not H_2O_2 in RAW264.7 cells nZnO induced O_2^- but not H_2O_2 in BEAS-2B cells. nZnO induced H_2O_2 in RAW264.7 and in HepG2 cells. Pretreatment with antioxidant N-acetylcysteine completely abolished cytotoxicity of ZnO in HepG2 cells. Overexpression of ROS-quenching enzyme MGST1 did not abolish toxicity of nZnO in MCF-7 cells. 10-30 nm nZnO induced more ROS than 30 and 100 nm ZnO in Ana-1 cells.	Karlsson et al. 2008; Kim et al. 2010; Sharma et al. 2012; Shi et al. 2012; Zhang et al. 2012
Depletion of GSH and lipid peroxidation	Lipid peroxidation preventing antioxidant vitamin E did not prevent nZnO-induced toxicity in HepG2 cells.	Li et al. 2012; Sharma et al. 2012; Guan et al. 2012
Regulation of ROS-quencing enzymes	Overexpression of heme oxygenase-1 in BEAS-2B cells exposed to ZnO. Inhibition of SOD activity.	Xia et al. 2008; Guan et al. 2012
DNA damage	nZnO induced oxidative DNA lessions in A549 cells. Pretreatment with antioxidant N-acetylcysteine mitigated DNA damage in HepG2 cells exposed to nZnO.	Karlsson et al. 2008; Sharma et al. 2012; Guan et al. 2012
Changes in cell morphology	See above the „Cellular uptake“	Xia et al. 2008; Sharma et al. 2012; Shi et al. 2012
Inflammation	Activation of IL-1, IL-8, AP-1 by both ZnO and ZnO supernatant in A549 cells. nZnO but not nZnO supernatant	Cho et al. 2012; Zhang et al. 2012

	recruited eosinophils. Activation of pro-inflammatory signaling pathway (Jun kinase) in BEAS-2B cells exposed to nZnO.	
Apoptosis/ Necrosis	Intracellular calcium release, mitochondrial membrane depolarization and release of pro-apoptotic factors in BEAS-2B cells. Collapse of mitochondrial membrane potential, mitochondrial swelling and damaged structural integrity in isolated rat liver mitochondria after exposure to ZnO. The mode of cell death in HepG2 cells exposured to ZnO was ROS-triggered mitochondria mediated apoptosis (Bax upregulation, Bcl2 down-regulation and JNKp38, p38, p53 and caspase-9 activation.	Xia et al. 2008; Li et al. 2012; Sharma et al. 2012

GSH – reduced glutathione, MGST1 - microsomal glutathione transferase 1, SOD-superoxide dismutase

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