is varied, which complicates understanding of the safety of nanomaterials. Interactions between biomolecules (such as lipids and proteins) and nanomaterials, to form the so-called corona, are assumed to affect the nanomaterials' biodistribution and biological effects [103]. Thus, it is necessary to reveal the factors that define the reproductive and developmental toxicity of nanomaterials by focusing not only on the physicochemical properties of the nanoparticle but also on the biomolecular corona. The NOAEL is not clear for many of the hazards described in this article. Therefore, determination of the NOAEL for each nanomaterial is also important.

References

1. Faustman EM, Silbernagel SM, Fenske RA, Burbacher TM, Ponce RA. Mechanisms underlying Children's susceptibility to environmental toxicants. Environ Health Perspect. 2000;108 Suppl 1:13–21.
2. Wigle DT, Arbuckle TE, Turner MC, Berube A, Yang Q, Liu S, et al. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. J Toxicol Environ Health B Crit Rev. 2008;11(5–6):373–517. doi:10.1080/10937400801921320.
3. Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MA, Van der Paauw CG, Tuinstra LG, Sauer PJ. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics. 1996;97(5):700–6.
4. Santos IS, Matijasevich A, Domingues MR. Maternal caffeine consumption and infant nighttime waking: prospective cohort study. Pediatrics. 2012;129(5):860–8. doi:10.1542/peds.2011-1773.
5. Fujimoto T, Kubo K, Nishikawa Y, Aou S. Postnatal exposure to low-dose bisphenol A influences various emotional conditions. J Toxicol Sci. 2013;38(4):539–46.
6. Healy DL, Trounson AO, Andersen AN. Female infertility: causes and treatment. Lancet. 1994;343(8912):1539–44.
7. Howards SS. Treatment of male infertility. N Engl J Med. 1995;332(5):312–17. doi:10.1056/NEJM199502023320507.
8. Franklin M, Zeka A, Schwartz J. Association between PM2.5 and all-cause and specific-cause mortality in 27 US communities. J Expo Sci Environ Epidemiol. 2007;17(3):279–87. doi:10.1038/sj.jes.7500530.
9. Hammoud A, Carrell DT, Gibson M, Sanderson M, Parker-Jones K, Peterson CM. Decreased sperm motility is associated with air pollution in Salt Lake City. Fertil Steril. 2010;93(6):1875–9. doi:10.1016/j.fertnstert.2008.12.089.
10. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry. 2013;70(1):71–7. doi:10.1001/jamapsychiatry.2013.266.
11. Delfino RJ, Sioutas C, Malik S. Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. Environ Health Perspect. 2005;113(8):934–46.
12. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. N Engl J Med. 2007;357(23):2348–58. doi:10.1056/NEJMoa071535.
13. Bowman DM, van Calster G, Friedrichs S. Nanomaterials and regulation of cosmetics. Nat Nanotechnol. 2010;5(2):92. doi:10.1038/nnano.2010.12.

14. Magnuson BA, Jonaitis TS, Card JW. A brief review of the occurrence, use, and safety of food-related nanomaterials. J Food Sci. 2011;76(6):R126–33. doi:10.1111/j.1750-3841.2011.02170.x.
15. Cheng Z, Al Zaki A, Hui JZ, Muzykantov VR, Tsourkas A. Multifunctional nanoparticles: cost versus benefit of adding targeting and imaging capabilities. Science. 2012;338 (6109):903–10. doi:10.1126/science.1226338.
16. Song Y, Li X, Du X. Exposure to nanoparticles is related to pleural effusion, pulmonary fibrosis and granuloma. Eur Respir J. 2009;34(3):559–67. doi:10.1183/09031936.00178308.
17. Liao HY, Chung YT, Lai CH, Lin MH, Liou SH. Sneezing and allergic dermatitis were increased in engineered nanomaterial handling workers. Ind Health. 2014;52(3):199–215.
18. Wu WT, Liao HY, Chung YT, Li WF, Tsou TC, Li LA, et al. Effect of nanoparticles exposure on fractional exhaled nitric oxide (FENO) in workers exposed to nanomaterials. Int J Mol Sci. 2014;15(1):878–94. doi:10.3390/ijms15010878.
19. Gao G, Ze Y, Li B, Zhao X, Zhang T, Sheng L, et al. Ovarian dysfunction and gene-expressed characteristics of female mice caused by long-term exposure to titanium dioxide nanoparticles. J Hazard Mater. 2012;243:19–27. doi:10.1016/j.jhazmat.2012.08.049.
20. Tassinari R, Cubadda F, Moracci G, Aureli F, D'Amato M, Valeri M, et al. Oral, short-term exposure to titanium dioxide nanoparticles in Sprague–Dawley rat: focus on reproductive and endocrine systems and spleen. Nanotoxicology. 2014;8(6):654–62. doi:10.3109/17435390.2013.822114.
21. Takahashi S, Matsuoka O. Cross placental transfer of 198Au-colloid in near term rats. J Radiat Res. 1981;22(2):242–9.
22. Semmler-Behnke M, Fertsch S, Schmid G, Wenk A, Kreyling. Uptake of 1.4 nm versus 18 nm gold nanoparticles in secondary target organs is size dependent in control and pregnant rats after intratracheal or intravenous application. In: EuroNanoForum 2007 – nanotechnology in industrial applications. 2007. Düsseldorf, Germany.
23. Yang H, Sun C, Fan Z, Tian X, Yan L, Du L, et al. Effects of gestational age and surface modification on materno-fetal transfer of nanoparticles in murine pregnancy. Sci Rep. 2012;2:847. doi:10.1038/srep00847.
24. Qi W, Bi J, Zhang X, Wang J, Wang J, Liu P, et al. Damaging effects of multi-walled carbon nanotubes on pregnant mice with different pregnancy times. Sci Rep. 2014;4:4352. doi:10.1038/srep04352.
25. Tsuchiya T, Oguri I, Yamakoshi YN, Miyata N. Novel harmful effects of [60]fullerene on mouse embryos in vitro and in vivo. FEBS Lett. 1996;393(1):139–45.
26. Sumner SC, Fennell TR, Snyder RW, Taylor GF, Lewin AH. Distribution of carbon-14 labeled C60 ([14C]C60) in the pregnant and in the lactating dam and the effect of C60 exposure on the biochemical profile of urine. J Appl Toxicol JAT. 2010;30(4):354–60. doi:10.1002/jat.1503.
27. Takeda K, Suzuki K, Ishihara A, Kubo-Irie M, Fujimoto R, Tabata M, et al. Nanoparticles transferred from pregnant mice to their offspring can damage the genital and cranial nerve systems. J Health Sci. 2009;55:95–102. doi:10.1248/jhs.55.95.
28. Yamashita K, Yoshioka Y, Higashisaka K, Mimura K, Morishita Y, Nozaki M, et al. Silica and titanium dioxide nanoparticles cause pregnancy complications in mice. Nat Nanotechnol. 2011;6(5):321–8. doi:10.1038/nnano.2011.41.
29. Tian F, Razansky D, Estrada GG, Semmler-Behnke M, Beyerle A, Kreyling W, et al. Surface modification and size dependence in particle translocation during early embryonic development. Inhal Toxicol. 2009;21 Suppl 1:92–6. doi:10.1080/08958370902942624.
30. Noori A, Parivar K, Modaresi M, Messripour M, Yousefi MH, Amiri GR, et al. Effect of magnetic iron oxide nanoparticles on pregnancy and testicular development of mice. Afr J Biotechnol. 2011;10(7):1221–7. doi:10.5897/AJB10.1544.
31. Melnik EA, Buzulukov YP, Demin VF, Demin VA, Gmoshinski IV, Tyshko NV, et al. Transfer of Silver Nanoparticles through the Placenta and Breast Milk during in vivo Experiments on Rats. Acta Nat. 2013;5(3):107–15.

32. Chu M, Wu Q, Yang H, Yuan R, Hou S, Yang Y, et al. Transfer of quantum dots from pregnant mice to pups across the placental barrier. Small. 2010;6(5):670–8. doi:10.1002/smll.200902049.
33. Sadauskas E, Wallin H, Stoltenberg M, Vogel U, Doering P, Larsen A, et al. Kupffer cells are central in the removal of nanoparticles from the organism. Part Fibre Toxicol. 2007;4:10. doi:10.1186/1743-8977-4-10.
34. Myllynen PK, Loughran MJ, Howard CV, Sormunen R, Walsh AA, Vahakangas KH. Kinetics of gold nanoparticles in the human placenta. Reprod Toxicol. 2008;26(2):130–7. doi:10.1016/j.reprotox.2008.06.008.
35. Zalgeviciene V, Kulvietis V, Bulotiene D, Didziapetriene J, Rotomskis R. The effect of nanoparticles in rats during critical periods of pregnancy. Medicina. 2012;48(5):256–64.
36. Wick P, Malek A, Manser P, Meili D, Maeder-Althaus X, Diener L, et al. Barrier capacity of human placenta for nanosized materials. Environ Health Perspect. 2010;118(3):432–6. doi:10.1289/ehp.0901200.
37. Grafmuller S, Manser P, Krug HF, Wick P, von Mandach U. Determination of the transport rate of xenobiotics and nanomaterials across the placenta using the ex vivo human placental perfusion model. J Vis Exp JoVE. 2013(76). doi:10.3791/50401.
38. Philbrook NA, Walker VK, Afrooz AR, Saleh NB, Winn LM. Investigating the effects of functionalized carbon nanotubes on reproduction and development in Drosophila melanogaster and CD-1 mice. Reprod Toxicol. 2011;32(4):442–8. doi:10.1016/j.reprotox.2011.09.002.
39. Pietroiusti A, Massimiani M, Fenoglio I, Colonna M, Valentini F, Palleschi G, et al. Low doses of pristine and oxidized single-wall carbon nanotubes affect mammalian embryonic development. ACS Nano. 2011;5(6):4624–33. doi:10.1021/nn200372g.
40. Fujitani T, Ohyama K, Hirose A, Nishimura T, Nakae D, Ogata A. Teratogenicity of multi-wall carbon nanotube (MWCNT) in ICR mice. J Toxicol Sci. 2012;37(1):81–9.
41. Blum JL, Xiong JQ, Hoffman C, Zelikoff JT. Cadmium associated with inhaled cadmium oxide nanoparticles impacts fetal and neonatal development and growth. Toxicol Sci. 2012;126(2):478–86. doi:10.1093/toxsci/kfs008.
42. Li PW, Kuo TH, Chang JH, Yeh JM, Chan WH. Induction of cytotoxicity and apoptosis in mouse blastocysts by silver nanoparticles. Toxicol Lett. 2010;197(2):82–7. doi:10.1016/j.toxlet.2010.05.003.
43. Chan WH, Shiao NH. Cytotoxic effect of CdSe quantum dots on mouse embryonic development. Acta Pharmacol Sin. 2008;29(2):259–66. doi:10.1111/j.1745-7254.2008.00743.x.
44. Hsieh MS, Shiao NH, Chan WH. Cytotoxic effects of CdSe quantum dots on maturation of mouse oocytes, fertilization, and fetal development. Int J Mol Sci. 2009;10(5):2122–35. doi:10.3390/ijms10052122.
45. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med. 2004;10(11):1222–6. doi:10.1038/nm1121.
46. Li Y, Wang HY, Cho CH. Association of heparin with basic fibroblast growth factor, epidermal growth factor, and constitutive nitric oxide synthase on healing of gastric ulcer in rats. J Pharmacol Exp Ther. 1999;290(2):789–96.
47. Hills FA, Abrahams VM, Gonzalez-Timon B, Francis J, Cloke B, Hinkson L, et al. Heparin prevents programmed cell death in human trophoblast. Mol Hum Reprod. 2006;12(4):237–43. doi:10.1093/molehr/gal026.
48. Hossain N, Schatz F, Paidas MJ. Heparin and maternal fetal interface: why should it work to prevent pregnancy complications? Thromb Res. 2009;124(6):653–5. doi:10.1016/j.thromres.2009.08.001.
49. Myatt L, Cui X. Oxidative stress in the placenta. Histochem Cell Biol. 2004;122(4):369–82. doi:10.1007/s00418-004-0677-x.
50. Shimizu M, Tainaka H, Oba T, Mizuo K, Umezawa M, Takeda K. Maternal exposure to nanoparticulate titanium dioxide during the prenatal period alters gene expression related to

brain development in the mouse. Part Fibre Toxicol. 2009;6:20. doi:10.1186/1743-8977-6-20.
51. Umezawa M, Tainaka H, Kawashima N, Shimizu M, Takeda K. Effect of fetal exposure to titanium dioxide nanoparticle on brain development – brain region information. J Toxicol Sci. 2012;37(6):1247–52.
52. Takahashi Y, Mizuo K, Shinkai Y, Oshio S, Takeda K. Prenatal exposure to titanium dioxide nanoparticles increases dopamine levels in the prefrontal cortex and neostriatum of mice. J Toxicol Sci. 2010;35(5):749–56.
53. Hougaard KS, Jackson P, Jensen KA, Sloth JJ, Loschner K, Larsen EH, et al. Effects of prenatal exposure to surface-coated nanosized titanium dioxide (UV-Titan). A study in mice. Part Fibre Toxicol. 2010;7:16. doi:10.1186/1743-8977-7-16.
54. Jackson P, Halappanavar S, Hougaard KS, Williams A, Madsen AM, Lamson JS, et al. Maternal inhalation of surface-coated nanosized titanium dioxide (UV-Titan) in C57BL/6 mice: effects in prenatally exposed offspring on hepatic DNA damage and gene expression. Nanotoxicology. 2013;7(1):85–96. doi:10.3109/17435390.2011.633715.
55. Fedulov AV, Leme A, Yang Z, Dahl M, Lim R, Mariani TJ, et al. Pulmonary exposure to particles during pregnancy causes increased neonatal asthma susceptibility. Am J Respir Cell Mol Biol. 2008;38(1):57–67. doi:10.1165/rcmb.2007-0124OC.
56. Yoshida S, Hiyoshi K, Oshio S, Takano H, Takeda K, Ichinose T. Effects of fetal exposure to carbon nanoparticles on reproductive function in male offspring. Fertil Steril. 2010;93(5):1695–9. doi:10.1016/j.fertnstert.2009.03.094.
57. Kyjovska ZO, Boisen AM, Jackson P, Wallin H, Vogel U, Hougaard KS. Daily sperm production: application in studies of prenatal exposure to nanoparticles in mice. Reprod Toxicol. 2013;36:88–97. doi:10.1016/j.reprotox.2012.12.005.
58. Jackson P, Vogel U, Wallin H, Hougaard KS. Prenatal exposure to carbon black (printex 90): effects on sexual development and neurofunction. Basic Clin Pharmacol Toxicol. 2011;109(6):434–7. doi:10.1111/j.1742-7843.2011.00745.x.
59. Jackson P, Hougaard KS, Vogel U, Wu D, Casavant L, Williams A, et al. Exposure of pregnant mice to carbon black by intratracheal instillation: toxicogenomic effects in dams and offspring. Mutat Res. 2012;745(1–2):73–83. doi:10.1016/j.mrgentox.2011.09.018.
60. Jackson P, Hougaard KS, Boisen AM, Jacobsen NR, Jensen KA, Moller P, et al. Pulmonary exposure to carbon black by inhalation or instillation in pregnant mice: effects on liver DNA strand breaks in dams and offspring. Nanotoxicology. 2012;6(5):486–500. doi:10.3109/17435390.2011.587902.
61. Umezawa M, Kudo S, Yanagita S, Shinkai Y, Niki R, Oyabu T, et al. Maternal exposure to carbon black nanoparticle increases collagen type VIII expression in the kidney of offspring. J Toxicol Sci. 2011;36(4):461–8.
62. Vitale R, Fawcett DW, Dym M. The normal development of the blood-testis barrier and the effects of clomiphene and estrogen treatment. Anat Rec. 1973;176(3):331–44.
63. Johanson CE. Permeability and vascularity of the developing brain: cerebellum vs cerebral cortex. Brain Res. 1980;190(1):3–16.
64. Chemes HE. Infancy is not a quiescent period of testicular development. Int J Androl. 2001;24(1):2–7.
65. Watson RE, Desesso JM, Hurtt ME, Cappon GD. Postnatal growth and morphological development of the brain: a species comparison. Birth Defects Res A Clin Mol Teratol. 2006;77(5):471–84. doi:10.1002/bdrb.20090.
66. Jonakait GM. The effects of maternal inflammation on neuronal development: possible mechanisms. Int J Dev Neurosci. 2007;25(7):415–25. doi:10.1016/j.ijdevneu.2007.08.017.
67. Gao X, Yin S, Tang M, Chen J, Yang Z, Zhang W, et al. Effects of developmental exposure to TiO2 nanoparticles on synaptic plasticity in hippocampal dentate gyrus area: an in vivo study in anesthetized rats. Biol Trace Elem Res. 2011;143(3):1616–28. doi:10.1007/s12011-011-8990-4.

68. De Jong WH, Hagens WI, Krystek P, Burger MC, Sips AJ, Geertsma RE. Particle size-dependent organ distribution of gold nanoparticles after intravenous administration. Biomaterials. 2008;29(12):1912–19. doi:10.1016/j.biomaterials.2007.12.037.
69. Balasubramanian SK, Jittiwat J, Manikandan J, Ong CN, Yu LE, Ong WY. Biodistribution of gold nanoparticles and gene expression changes in the liver and spleen after intravenous administration in rats. Biomaterials. 2010;31(8):2034–42. doi:10.1016/j.biomaterials.2009.11.079.
70. Li WQ, Wang F, Liu ZM, Wang YC, Wang J, Sun F. Gold nanoparticles elevate plasma testosterone levels in male mice without affecting fertility. Small. 2013;9(9–10):1708–14. doi:10.1002/smll.201201079.
71. Bai Y, Zhang Y, Zhang J, Mu Q, Zhang W, Butch ER, et al. Repeated administrations of carbon nanotubes in male mice cause reversible testis damage without affecting fertility. Nat Nanotechnol. 2010;5(9):683–9. doi:10.1038/nnano.2010.153.
72. Gao G, Ze Y, Zhao X, Sang X, Zheng L, Ze X, et al. Titanium dioxide nanoparticle-induced testicular damage, spermatogenesis suppression, and gene expression alterations in male mice. J Hazard Mater. 2013;258–259:133–43. doi:10.1016/j.jhazmat.2013.04.046.
73. Zhao X, Sheng L, Wang L, Hong J, Yu X, Sang X, et al. Mechanisms of nanosized titanium dioxide-induced testicular oxidative stress and apoptosis in male mice. Part Fibre Toxicol. 2014;11(1):47. doi:10.1186/s12989-014-0047-3.
74. Morishita Y, Yoshioka Y, Satoh H, Nojiri N, Nagano K, Abe Y, et al. Distribution and histologic effects of intravenously administered amorphous nanosilica particles in the testes of mice. Biochem Biophys Res Commun. 2012;420(2):297–301. doi:10.1016/j.bbrc.2012.02.153.
75. Zhu MT, Feng WY, Wang Y, Wang B, Wang M, Ouyang H, et al. Particokinetics and extrapulmonary translocation of intratracheally instilled ferric oxide nanoparticles in rats and the potential health risk assessment. Toxicol Sci. 2009;107(2):342–51. doi:10.1093/toxsci/kfn245.
76. Kim YS, Song MY, Park JD, Song KS, Ryu HR, Chung YH, et al. Subchronic oral toxicity of silver nanoparticles. Parti Fibre Toxicol. 2010;7:20. doi:10.1186/1743-8977-7-20.
77. Park EJ, Bae E, Yi J, Kim Y, Choi K, Lee SH, et al. Repeated-dose toxicity and inflammatory responses in mice by oral administration of silver nanoparticles. Environ Toxicol Pharmacol. 2010;30(2):162–8. doi:10.1016/j.etap.2010.05.004.
78. van der Zande M, Vandebriel RJ, Van Doren E, Kramer E, Herrera Rivera Z, Serrano-Rojero CS, et al. Distribution, elimination, and toxicity of silver nanoparticles and silver ions in rats after 28-day oral exposure. ACS Nano. 2012;6(8):7427–42. doi:10.1021/nn302649p.
79. Lee JH, Kim YS, Song KS, Ryu HR, Sung JH, Park JD, et al. Biopersistence of silver nanoparticles in tissues from Sprague–Dawley rats. Part Fibre Toxicol. 2013;10:36. doi:10.1186/1743-8977-10-36.
80. Yokel RA, Au TC, MacPhail R, Hardas SS, Butterfield DA, Sultana R, et al. Distribution, elimination, and biopersistence to 90 days of a systemically introduced 30 nm ceria-engineered nanomaterial in rats. Toxicol Sci. 2012;127(1):256–68. doi:10.1093/toxsci/kfs067.
81. Kim JS, Yoon TJ, Yu KN, Kim BG, Park SJ, Kim HW, et al. Toxicity and tissue distribution of magnetic nanoparticles in mice. Toxicol Sci. 2006;89(1):338–47. doi:10.1093/toxsci/kfj027.
82. Kwon JT, Hwang SK, Jin H, Kim DS, Minai-Tehrani A, Yoon HJ, et al. Body distribution of inhaled fluorescent magnetic nanoparticles in the mice. J Occup Health. 2008;50(1):1–6.
83. Wang Z, Chen Z, Zuo Q, Song F, Wu D, Cheng W, et al. Reproductive toxicity in adult male rats following intra-articular injection of cobalt-chromium nanoparticles. J Orthop Sci. 2013;18(6):1020–6. doi:10.1007/s00776-013-0458-2.
84. Araujo L, Sheppard M, Löbenberg R, Kreuter J. Uptake of PMMA nanoparticles from the gastrointestinal tract after oral administration to rats: modification of the body distribution

after suspension in surfactant solutions and in oil vehicles. Int J Pharm. 1999;176(2):209–24. doi:10.1016/S0378-5173(98)00314-7.
85. Yoshida S, Hiyoshi K, Ichinose T, Takano H, Oshio S, Sugawara I, et al. Effect of nanoparticles on the male reproductive system of mice. Int J Androl. 2009;32(4):337–42. doi:10.1111/j.1365-2605.2007.00865.x.
86. Sycheva LP, Zhurkov VS, Iurchenko VV, Daugel-Dauge NO, Kovalenko MA, Krivtsova EK, et al. Investigation of genotoxic and cytotoxic effects of micro- and nanosized titanium dioxide in six organs of mice in vivo. Mutat Res. 2011;726(1):8–14. doi:10.1016/j.mrgentox.2011.07.010.
87. Hassankhani R, Esmaeillou M, Tehrani AA, Nasirzadeh K, Khadir F, Maadi H. In vivo toxicity of orally administrated silicon dioxide nanoparticles in healthy adult mice. Environ Sci Pollut Res Int. 2015;22(2):1127–32. doi:10.1007/s11356-014-3413-7.
88. Gromadzka-Ostrowska J, Dziendzikowska K, Lankoff A, Dobrzynska M, Instanes C, Brunborg G, et al. Silver nanoparticles effects on epididymal sperm in rats. Toxicol Lett. 2012;214(3):251–8. doi:10.1016/j.toxlet.2012.08.028.
89. Li C, Taneda S, Taya K, Watanabe G, Li X, Fujitani Y, et al. Effects of inhaled nanoparticle-rich diesel exhaust on regulation of testicular function in adult male rats. Inhal Toxicol. 2009;21(10):803–11. doi:10.1080/08958370802524381.
90. Ramdhan DH, Ito Y, Yanagiba Y, Yamagishi N, Hayashi Y, Li C, et al. Nanoparticle-rich diesel exhaust may disrupt testosterone biosynthesis and metabolism via growth hormone. Toxicol Lett. 2009;191(2–3):103–8. doi:10.1016/j.toxlet.2009.08.013.
91. Guo LL, Liu XH, Qin DX, Gao L, Zhang HM, Liu JY, et al. Effects of nanosized titanium dioxide on the reproductive system of male mice. Zhonghua nan ke xue = Nat J Androl. 2009;15(6):517–22.
92. Wiwanitkit V, Sereemaspun A, Rojanathanes R. Effect of gold nanoparticles on spermatozoa: the first world report. Fertil Steril. 2009;91(1):e7–8. doi:10.1016/j.fertnstert.2007.08.021.
93. Ben-David Makhluf S, Qasem R, Rubinstein S, Gedanken A, Breitbart H. Loading magnetic nanoparticles into sperm cells does not affect their functionality. Langmuir. 2006;22(23):9480–2. doi:10.1021/la061988z.
94. Braydich-Stolle LK, Lucas B, Schrand A, Murdock RC, Lee T, Schlager JJ, et al. Silver nanoparticles disrupt GDNF/Fyn kinase signaling in spermatogonial stem cells. Toxicol Sci. 2010;116(2):577–89. doi:10.1093/toxsci/kfq148.
95. Terzuoli G, Iacoponi F, Moretti E, Renieri T, Baldi G, Collodel G. In vitro effect of silver engineered nanoparticles on human spermatozoa. J Siena Acad Sci. 2011;3(1):27–9. doi:10.4081/jsas.2011.27.
96. Zakhidow ST, Marshak TL, Malolina EA, Kulibin AY, Zelenina IA, Pavluchenkova SM, et al. Gold nanoparticles disturb nuclear chromatin decondensation in mouse sperm in vitro. Biochem (Moscow) Suppl Ser A Membr Cell Biol. 2010;4(3):293–6. doi:10.1134/S1990747810030074.
97. Carone BR, Fauquier L, Habib N, Shea JM, Hart CE, Li R, et al. Paternally induced transgenerational environmental reprogramming of metabolic gene expression in mammals. Cell. 2010;143(7):1084–96. doi:10.1016/j.cell.2010.12.008.
98. Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ. Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. Nature. 2010;467(7318):963–6. doi:10.1038/nature09491.
99. Dias BG, Ressler KJ. Parental olfactory experience influences behavior and neural structure in subsequent generations. Nat Neurosci. 2014;17(1):89–96. doi:10.1038/nn.3594.
100. Gapp K, Jawaid A, Sarkies P, Bohacek J, Pelczar P, Prados J, et al. Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nat Neurosci. 2014;17(5):667–9. doi:10.1038/nn.3695.
101. Bal R, Turk G, Tuzcu M, Yilmaz O, Ozercan I, Kuloglu T, et al. Protective effects of nanostructures of hydrated C(60) fullerene on reproductive function in streptozotocin-diabetic male rats. Toxicology. 2011;282(3):69–81. doi:10.1016/j.tox.2010.12.003.

102. Srdjenovic B, Milic-Torres V, Grujic N, Stankov K, Djordjevic A, Vasovic V. Antioxidant properties of fullerenol C60(OH)24 in rat kidneys, testes, and lungs treated with doxorubicin. Toxicol Mech Methods. 2010;20(6):298–305. doi:10.3109/15376516.2010.485622.
103. Lundqvist M, Stigler J, Elia G, Lynch I, Cedervall T, Dawson KA. Nanoparticle size and surface properties determine the protein corona with possible implications for biological impacts. Proc Natl Acad Sci U S A. 2008;105(38):14265–70. doi:10.1073/pnas.0805135105.

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Chapter 4
Reproductive and Developmental Effects of Nanomaterials

Yuki Morishita, Yasuo Yoshioka, Kazuma Higashisaka, and Yasuo Tsutsumi

Abstract Reproductive and developmental toxicity are among the most important factors for evaluating the safety of chemical substances. Some critical organs for reproduction are protected by biological barriers: the fetus is protected by the blood–placental barrier and the testes by the blood–testis barrier. The small size of nanomaterials affords them unique biodistribution characteristics and thus biological effects that differ from those of larger materials. Their small size might allow nanoparticles to penetrate barriers and cause unexpected reproductive and developmental toxicity. In this chapter, the reproductive and developmental toxicity of nanomaterials, including biodistribution within and biological effects on reproductive tissues, fetuses, and offspring, are reviewed. Investigations show that nanomaterials can penetrate biological barriers and can be distributed to the ovaries, testes, and fetuses of rodents. Nanomaterials thus have the potential to affect both male and female reproductive functions. Maternal exposure to nanomaterials during gestation or lactation could also adversely affect the fetus

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T. Otsuki et al. (eds.), *Biological Effects of Fibrous and Particulate Substances*,
Current Topics in Environmental Health and Preventive Medicine,
DOI 10.1007/978-4-431-55732-6_4

Chapter 9

Biocompatibility of Nanomaterials

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Abstract

Remarkable progress has been made in the field of nanotechnology in the past decade. Many new nanoparticles, which are defined as particles with at least one dimension between 1 and 100 nm, have been created, and new medical applications for these nanoparticles are now expected. To be able to create effective and safe nanomedicines, more information is needed about the effects and safety of nanoparticles in vivo because physical properties such as material composition, particle size, surface area, surface chemistry, surface charge, and agglomeration state all influence nanoparticle biocompatibility, particularly with regard to activation of the complement, coagulation, and immune systems. In this chapter, we introduce the most recent developments in our understanding of the biocompatibility of nanoparticles and discuss how our current understanding translates to the field of nanomedicine.

Key words Coagulation, Complement, Immune response, Nanomedicine, Protein corona, Safety, Surface property, Toxicity

1 Introduction

Recent progress in the field of nanotechnology means that it is now possible to produce a wide variety of nanoparticles, which are particles that have at least one dimension between 1 and 100 nm. Compared with larger particles of the same material, nanoparticles have a larger surface area per unit weight, which produces desirable properties such as enhanced electrical conductivity, tensile strength, and chemical reactivity. Nanoparticles are already being used in the electronics, food, cosmetics, and medical industries. In the medical industry, the application of nanotechnology (nanomedicine) is expected to provide novel diagnostic and imaging technologies, photothermal therapies, and vaccine and drug delivery systems for poorly soluble or unstable drugs. Unlike larger, micrometer-sized particles, nanoparticles are small enough to be absorbed through biological barriers and therefore can enter almost all of the body's compartments, including cells and intracellular organelles. Furthermore, the targeting of nanoparticles to specific pathological sites may reduce the incidence of side effects by increasing drug

Zheng-Rong Lu and Shinji Sakuma (eds.), *Nanomaterials in Pharmacology*, Methods in Pharmacology and Toxicology,
DOI 10.1007/978-1-4939-3121-7_9,