Quantifying the biodistribution of nanoparticles

To the Editor — Yamashita *et al.* (*Nature Nanotech.* **6,** 321–328; 2011) report that silica and titanium dioxide (TiO_2) nanoparticles with diameters of 70 nm and 35 nm, respectively, can cross the placental barrier in pregnant mice. Using transmission electron microscopy (TEM), the researchers claim that nanoparticles are found in the liver and brain of the fetus[1]. Although TEM is useful for the qualitative examination of nanoparticles, it is not sensitive enough for studying the trans-placental transport of TiO_2 nanoparticles.

Assuming that the concentration of TiO_2 nanoparticles in the fetal liver is one nanogram per gram of liver (the density of liver is approximately 1.1 g cm^{-3}) and that the mass of a 35 nm TiO_2 particle is approximately 1×10^{-16} g (the density of rutile-TiO_2 is 4.3 g cm^{-3}), on average, only one nanoparticle can theoretically be found in a 1 mm^2 section of liver tissue (an ultrathin section usually has a thickness of less than 100 nm). The TEM images collected by Yamashita *et al.* showed a dark electron-dense spot in a field size of ~5 μm × 5 μm. Based on our estimation, on average, tens of thousands of such images need to be examined to find one TiO_2 nanoparticle. This means that the TEM results cannot firmly prove that nanoparticles were present in the fetal liver and brain, unless the concentration of nanoparticles in the fetal liver is several orders of magnitude higher than the hypothetical value of one nanogram per gram.

In conclusion, more suitable quantitative methods should be used to study the biodistribution of nanoparticles in pregnant mice. ❐

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To the Editor — In general, transmission electron microscopy (TEM) and quantitative methods such as inductively coupled plasma-mass spectrometry (ICP-MS) are used to study the biodistribution of nanomaterials. For example, ICP-MS can detect the elements of nanomaterials and evaluate their biodistribution quantitatively. However, ICP-MS cannot distinguish between elements that are inherent to the nanomaterials and those that are cleaved or released from them. But, unlike ICP-MS, TEM can detect the presence of nanomaterials and identify their location within tissues and cells. Even though the TEM images in our study[1] provide only qualitative information, TEM is invaluable for identifying the biodistribution of the silica and TiO_2 nanoparticles.

He *et al.*[2] correctly point out the detection limit of TEM and that only some silica and TiO_2 nanoparticles could be detected in the small section of the placental and fetal tissue in our study. However, through analysis of several hundreds of TEM sections, we confirmed that silica and TiO_2 nanoparticles did accumulate in both the placental and fetal tissues. The observations were not coincidental.

To study the biodistribution of nanomaterials quantitatively, methods such as ICP-MS should be used and, indeed quantitative biodistribution studies of silica and TiO_2 nanoparticles in the mouse placenta and fetus are currently under way in our laboratory. ❐

References
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