Reviews

New development of study on the toxicity of nano materials

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Abstract Toxicity reseach of nano materials not only has very important significance to human health, but also concerns labour protection and resource utilization etc., so it should be highly regarded by our government. This article overviews it from medicine, and expounds the significance of the toxicity estimate for nano materials according to the change of physico–chemical property after macroscopic materials be made to nano materials, it proposes that we should not ignore the potential influence on health and the necessity of investigation in the development of nanotechnology ,so that people can exactly recognize and reasonably utilize nano materials.

Keywords: nano material; toxicity; development

International science generally considers that nanotechnology, infotechnology and life science will be three strong foothold of technology development in 21st technology. As considerable economy profit and technological progress brought by nanotechnology and nanomaterials, studies and correlated investigations at home and abroad are very considerable. However, at present studies and correlative information about toxicity evaluation on nano materials are very scarce. From the point of toxicology, nearly all materials have potential toxicity to human, the key point is its dose and route of exposure. With the professional sensitivity, we should calmly consider the far reaching influence that nano materials will take to human health.

Food and Drug Administration (FDA) claims that any new product must pass standard check and be proved its security, effectiveness and possibility of plentiful production. Recently, National Science Foundation (NSF) and Environmental Protection Agency (EPA) have confirmed some topic on safety evaluation of nano materials[1]: (1) exposure evaluation of nano materials; (2) toxicology of artificial nano particle; (3) possibility of using toxicologic data of known particles and fibers to extrapolate toxicity of artificial nano particle; (4) circumstance of nano materials and biologic turnover, diversion, residual, transformation and metabolism; (5) retrieval and salvageof nano materials.

1 Definition, characteristics and medical application of nano materials

Nano meter (nm) is a scale unit, a nano meter is equal to 10^{-9} meter . Nanomaterial has special function and its geometric size reaches to nano level. Its characteristics is that quanta size effect, microsize effect, superficial and interfacial effect, macroquanta quantum leakage. The nano material has been deeply concerned in medical area, for example as a drug carrier, we can mainly use it to destroy tumor cells to realize drug´s targeted therapy; analyzing biomolecule (as protein) by using nano–scale exosyndrome measurement technology, we can apply it to research nano–scale ware minisystem as medical diagnosis and surgery assisted robot; wecan develop nano biomimetic materials which can be used to diagnose and treat focuses of infection in vivo (for example: rebuilding autogenous bone, artificial kidney, artificial joint in Tissue Engineering, having good antibiosis and hemostasis effect in material engineering).

2 Overseas study progress of nano material toxicity

2.1 Adri amycin polycyanoacrylate nano particle (APNP)

Russian scientists discovered that APNP could bring

adriamycin through blood brain barrier after intravenous injection to inhibit tumor growth in rat brain. If only intravenous injecting polycyanoacrylate nano particle, dose 100–400 mg/kg, it did not lead to death of rats in observation period and did not effect rats weight and interior organs. The results could demonstrate that toxicity of adriamycin packed by polycyanoacrylate nano particle did not change, even was less than unpacked adriamycin

2.2 Fullerene

Fullerene is a nano material. Animal studies discovered that cutaneous toxicity of fullerene was very small, but more studies found that intravenous injecting fullerene would appear acute toxicity [4]. A hydrosoluble fullerene, its median lethal dose (LD50) of intraperitoneal injection is 600 mg/kg, abnormal renal injury can be observed at low dose[5]. However , hydrosoluble fullerene is a bioactive material, its hydroxylation derivation can clear up free radicles in vivo, can inhibit keratinocyte proliferation, can protect human keratinocyte from apoptosis mediated by UVB, can protect cytochondriome from depolarization irradiated by UVB [6]. Foley *et al* [7] found that fullerene derivation C61 $(COOH)_2$ could penetrate cytomembrane to combine with cytochondriome ,as intracellular active oxyradical came from electrontransfer chain in cytochondriome , fullerene clearing up intracell free radicles might be related to the combination .

2.3 Influence of nano particle on respiratory tract and pulmonary alveolus

In 1994 report, International Commission on Radiological Protection (ICRP) indicated that nano particle could deposit to human respiratory tract and pulmonary alveolus, which has been confirmed by recent studies. Particles, which size are 1 nm, 90% of them would deposit to pharynx nasalis, the other 10% would deposit to tracheobronchial and scarcely deposit to pulmonary alveolus. As for 5–10 nm size particle, deposition of above mentioned 3 parts is all 20–30%; As for 20 nm size particle, about 50% would deposit to pulmonary alveolus, which demonstrates that nano particles´ deposition sites in human respiratory tract are related to size. Although mass concentration of nano materials breathed in body is not high, their sizes are very small and quantities are very large, all of that provide possibility of nano particles to lead lung lesion.

It is found that nano particles can lead to obvious alveolar macrophage (AM) lesion. Renwick et al[13] observed that rat AM was cultivated 8 hours insubstratum contained nano coom (14.3 nm) and nano $Ti0_2$ (29.0 nm), its phagocytosis ability was obviously inhibited . Lundborg et al [14] exposed healthy volunteers' AM to 0.03–3 $\mu g/10^6$ size nano carbon particles , they found that AM' ssticking and phagocytosis function to $Si0_2$ particles were inhibited. Zhang and kusaka[15] incubated AM in substratum contained nano TiO_2, nano Ni, nano Co and found that activity of LDH and TNF–2 in every dose group supernatant presented dose response relation, which demonstrated that nano particles have injured AM cytomembrane.

2.4 Nano particle size and bo dy toxic reaction

P.K. Gupta, K.J. Widder, et al [16,17] proved that nano medicine , size between 100–200 nm, was phagocytized by endotheliocyte after administering 10 minutes and seen in ectovessel gaps at 30 minute. The medicine enters into cells mainly by phagocytosis and as its large molecular weight, it can not easily enter into myocardium and gastrointestinal mucosa cells and can gather in reticuloendothelialsystem organs such as liver and spleen, which can realize its target treatment and reduce toxicity and side effect. Oberdorster, a toxicologist from University of Rochester School of Medicine and Dentistry in New York, reported that exposed 15 minute in air contained PTFE nano particles of mean diameter 18 nm, most animals had acute lung lesion and died in 4 hours; but exposed in air contained PTFE particles which size were greater than 130 nm, they did not have toxic reaction [18].

It demonstrates that even mini–toxicity matter at routine size, when it reaches to nanometer class condition, its biological effects also have fundamental changes.

2.5 Diversion of nano materials in vivo

When macroscopic matter is made to nano material , as its minimum size, its surface binding energy and chemical activity obviously enhance. Matter composition does not have change, but its biological effect and effect intension tobody may have essential changes. Entering into organism, nano materials can transfer to surrounding tissue even farther. Diversion mode mostly observed is one from respiratory tract surface to submucous tissue. Oberdorster [19] et al found that ratsexposing 4 hours to 20 nm

size polytetrafluoroethylene (PTFE), PTFE had entered into respiratory tract submucosa and alveolus interstitium. Lam[20] and Warheit[21] also observed that single-walled carbon nanotubes (SWNT) transfered into interstitial tissue of animal lung. Moreover , Oberdorster et al [22] made rats breathedin ^{13}C grains (30 nm), after 24 hours they had found many ^{13}C gained in rats' livers, which demonstrated that nano ^{13}C grains can quickly enter into circulation-system. WANG, et al [23] gave rats SWNT labeled by radioactive ^{125}I by differentways such as intragastric administration, intraperitoneal injection and intravenous injection, SWNT could quickly distribute to rats each organs and tissues (except cerebrum), showing that SWNT, its relative molecular mass greater than 600,000, could freely shuttle back and forth in every parts of body like micromolecule, which was different from routine matter. Whether can nano materials break through blood brain barrier to enter into central nervous system? Kreuter [24] found that adriamycin nano particles contained by polysorbate 80 through intravenous injection couldbreak through rat blood brain barrier and had effect on intracal grafting gliocytoma. They believed that nano particles were phagocytized by cerebrum capillary endothelium cells into cerebrum. Oberdorster et al [25] found another possible pathway to central nervous system — olfactory nerves pathway.

Besides relative easily entering into body, nano materials can easily permeateventage on biomembrane into cells or organoids including chondrosome, endoplasmic reticulum, lysosome, golgiosome and cell nucleus, and occur combination or catalysis chemical reactions with biomacromolecules that make normal stereochemical structure of biomacromolecule and biomembrane changed. The result may lead to devitalization of some hormones and important enzyme systems in vivo, or make genetic material mutated resulting in increasing tumor incidence or promoting ageing. At present, these apprehensions are potential adverse effect presumed from special property of nano materials, but we have not had enough evidences to deny these harmful effects.

All of those have shown that nano materials can transfer in vivo after enteringinto body, so it is necessary to deeply study its toxico-kinetics. The fact also hints that previous safety evaluation results of macro-matter maybe not refer to nano material.

3 Relative study in China

At present, our scholars have almost kept pace with international on the studiesof nano materials toxicity, and have gained some achievements under financial assistance of great projects as National Natural Science Foundation of China (NSFC).

Nano magnetic materials re ones which have strong magnetism, simple preparation and good biocompatibility, so that there are eneral applications in biomedicine domain. Acute toxicity test of intravenous galactosyl-HSA-magnetic-adriamycin-nanoparticles, taken by ZHANG Yangde et al [27], showed that galactosyl-HSA-magnetic-adriamycin-nanoparticles was a very good new type improved medicine, Its LD50 calculated from experiments was 515.5 mg/kg (corresponded to pure adriamycin 22.84 mg/kg), which had more obvious improvement than adriamycin LD50 (10.38 mg/kg) provided by pharmaceutical factory and obviously relieved drug's side effect to heart and kidney. MA Ming et al [28] tested toxicity of anticancer materials made by spheric r-Fe_2O_3 and Fe_3O_4 magnetic-nanoparticles which covered by glutamate molecular on surface, and had not found Fe_2O_3 magnetic-nanoparticles had genetoxic effect on mammal's somatocyte and gonoblast. After 14-day's successive administration , the materials' non-toxic reaction dose was more 10 times than body recommended injection dose. Fe_2O_3 magnetic-nanoparticles did not have mutagenic action on somatocyte, but it might have mutagenic actionon male gonoblast administered by mouth.

WANG Tiancheng group proceeded acute toxicity testing on animals with nano iron. They administered rats by mouth respectively with nano pulvis aci and routine size pure pulvis aci at a fixative dose 5 g/kg, observing 14 days, they found no ratsdied, and no abnormality seen on rats, which showed that at the test dose nanopulvis aci and routine pulvis aci both belonged to fundamental non-toxicity materials. Influence of nano pulvis aci at large dose on organism metabolism and someserum biochemical indicator is different from common iron materials, which hints that common biochemical indicator suitable for toxicity assessment of routine particle size materials may be not applicable to the one of nano materials and it is

necessary to look for and build a new assessment system.

4 Discussion and Summary

1) There are significant research values that what toxicity changes nano materials will take place on different outside conditions (as different charge, different physico-chemical property) and how to alter toxicity of nano materials by changing outside conditions.

2) There are significant connection between nano particles' toxicity and size. It ispossible that when size diminishes to certain extent, previous non-toxicity or less toxicity nano materials begin to have toxicity or more. Therefore, It should be paid more attention to toxicity comparison between same kind nano materials with different size.

3) Some nano materials can break through parts in organism that another materials are hard to do, as blood brain barrier, blood-ocular barrier, blood-testis-barrier and placental barrier. Thus, in vivo nano materials may occur some special metabolic condition to bring some special toxicity.

4) Some size nano grains can massively enter into cells, it is deserved to discuss how they penetrate cytomembrane into cells and how they develop toxic action.

5) From different observation levels, nano materials have different level of influenceon animals and their organs, tissues, cells, molecules and genes, It is interested in which level of influence best deserved to pay attention to and correlations among them.

6) Nano materials are different from another traditional materials due to its mini-size. Thus, research methods, which are different from another traditional materials, can be used to study mechanism of toxic action and to institute special safety evaluation criterion of nano materials.

5 Conclusions

In the rapid development of nanometer tide, we can not ignore anything all has dualism. Strictly speaking, the research results are very initial, present ownedstudy data are very limit. Just because of those, it is easily thought by mistake that all nano materials have huge toxicity, there is a long time before eliminating misunderstanding and gaining accurate, objective, responsible scientific conclusion.

Gratifiedly, nano technology research is a topic studied its toxicity for the firsttime in human history before technology maturating and industrialization forming. Scientificly evaluation and anticipation toxicity of nano materials still need deep, systemic and long-term research and need real discipline cross of each study methodssuch as biotechnology, nano-technology, medicine, chemistry and physics.

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