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Review

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Safe Bloodstream Concentration Limits for Microscale Nanorobots

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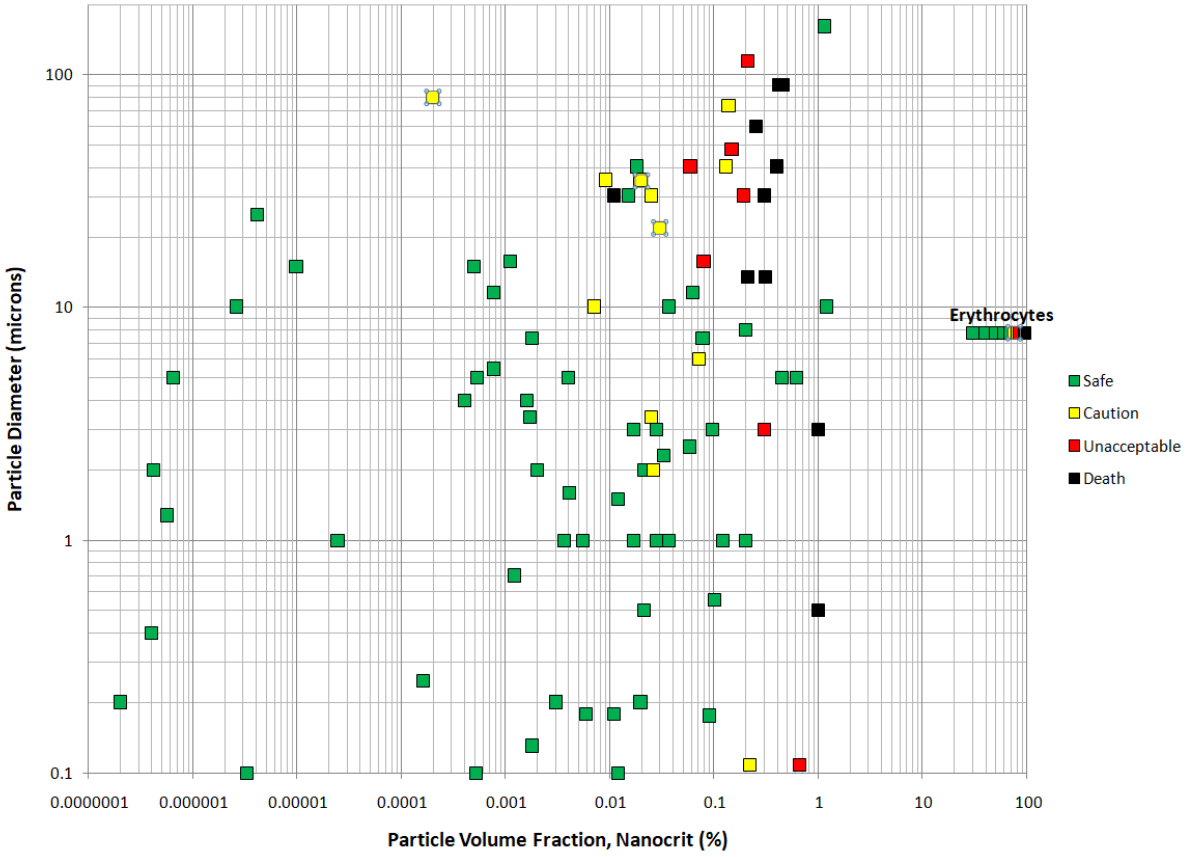
Graphical Abstract



Abstract

The greatest power of nanomedicine will emerge as we learn to design and construct complete artificial nanorobots using nanometer-scale parts and onboard subsystems such as diamondoid bearings and gears, nanomotors and molecular pumps, nanomanipulators, nanosensors, nanobatteries, and nanocomputers. However, according to initial human intravenous tests of future microscale diamondoid nanorobots in the 0.5-3 μm size range should not exceed a maximum bloodstream volumetric concentration of ~0.001%.

Keywords

Nanorobot, bloodstream concentration, safety, nanoparticle, microparticle, diamondoids, humans

Purpose, Rationale, and Limitations

The emergence of atomically precise manufacturing and nano-factories[1] will eventually make possible the design and manufacture of molecular machine systems, including sophisticated micron-scale medical nanorobots,[2] possibly constructed of atomically precise diamondoids or similar crystalline ceramic materials[3] for a wide variety of powerful applications.[4]

Before such robots could be considered for clinical practice, their safety when injected into the bloodstream of animal or human subjects would have to be established, leaving aside the

further analysis of the likely mechanical and kinematic activities of such active-dimensioned devices[5] and considering them simply as passive rigid microparticles in our initial evaluation.

Introduction

Many experimental studies in animal and human subjects over the last 70 years have directly studied, or have reported as indirect outcomes of related studies, the pathological effects of intravenous injection of microparticles of various sizes and compositions. Definitive safe ranges cannot yet be specified. Still, a maximum safe concentration limit for well-engineered future nanorobots derived from reported experimental results using only the coarsely-shaped passive microparticles surveyed here should provide at least a conservative upper limit. This is because sophisticated future nanorobots will be specifically designed to avoid basic biocompatibility problems[6] such as accumulation in capillary beds, whereas the passive microparticles in existing studies were not. Additional caution is warranted because the historical literature's descriptions of outcomes and pathologies have been relatively crude and qualitative.

Many clinical effects have been documented in patients who have received therapeutic injections containing particulate matter contamination,[7] including infusion-related phlebitis,[8] pulmonary emboli,[9] pulmonary granulomas,[10] foreign body reactions from glass particle contaminants,[11] immune system dysfunction,[12] pulmonary dysfunction,[13] adult respiratory distress syndrome,[14] systemic inflammatory response syndrome (SIRS),[15] infarction,[16] and even death.[17] Hard particles >5 μm in size are more likely to produce mechanical obstruction and vascular emboli.[18] A previously published literature survey[19] found almost exclusive coverage of cell responses to diamondoid particulates but almost no tissue, organ, or whole-body data. Literature data on the bloodstream safety of nontoxic metabolically inert particles are summarized in Figure 1 and Table 1.

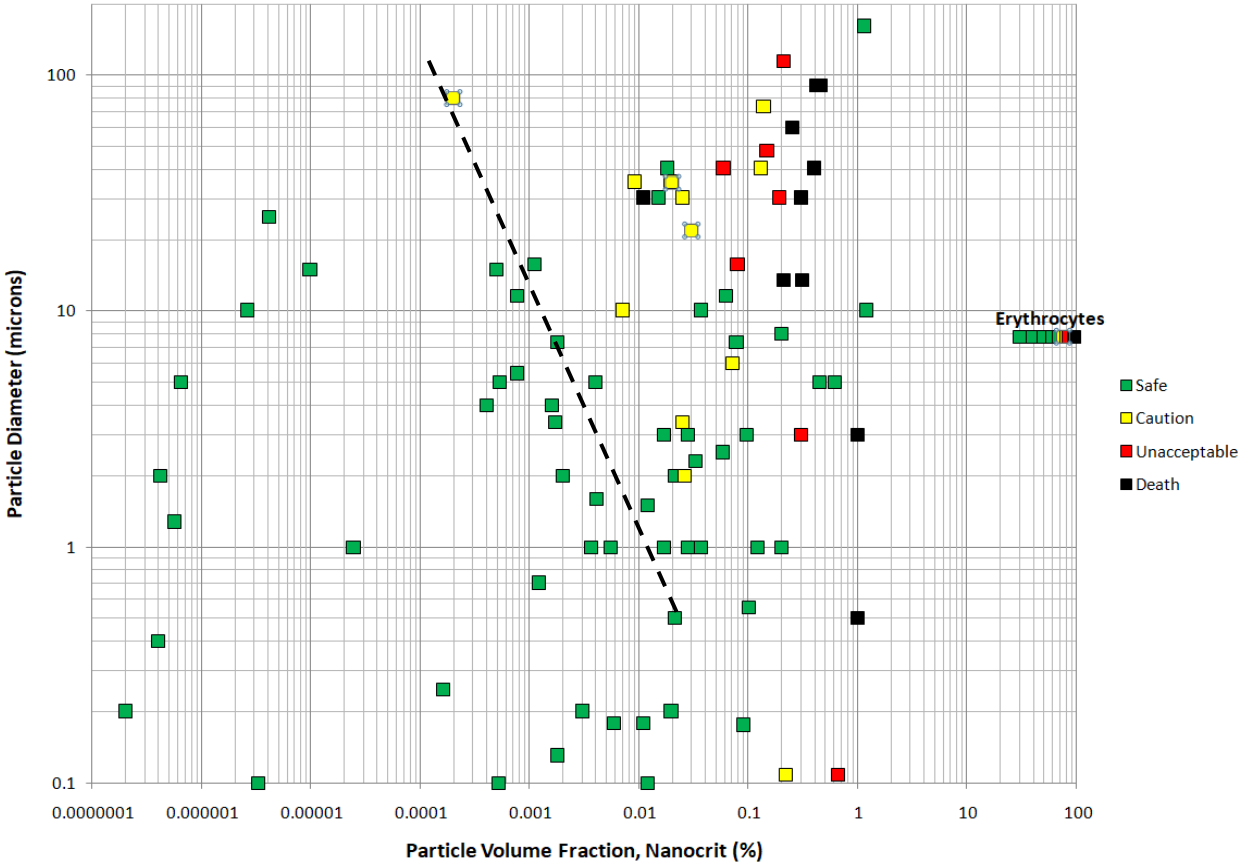


Figure 1. Microparticle safety as a function of diameter and bloodstream concentration

Table 1. Microparticle bloodstream bio-tolerance in animals and humans

Particle Size and Type	Tester	Max. Concentration (Nct)		Reported Consequences
0.2/1/4 µm polystyrene micro-spheres[20]	rat	2 x 10^{-7} % / 2.5 x 10^{-5} % / 0.0016%		no reported discomfort
1.27/15.8 µm polystyrene micro-spheres[21]	rabbit	5.6 x 10^{-7} % / 0.0011%		no adverse effects
>2 µm particle contaminants[22]	human	4.2 x 10^{-7} %		1980 British Pharmacopoeia: safe
>5 µm particle contaminants[23]	human	6.5 x 10^{-7} %		1980 British Pharmacopoeia: safe
>10 µm particle contaminants[24]	human	2.6 x 10^{-6} %		1990 British Pharmacopoeia: safe
>25 µm particle contaminants[25]	human	4.1 x 10^{-6} %		1990 British Pharmacopoeia: safe
~15 µm ^{99m}Tc albumin micro-spheres[26]	human	1 x 10^{-5} %		no toxicity or antibody formation
0.1/0.25 µm gold nanoparticles[27]	rat	3.3 x 10^{-6} % / 0.00016%		no reported discomfort
0.11 µm silver nanoparticles[28]	rat	1.5 x 10^{-5} %		no adverse effects
10 x 80 µm cotton filter paper[29]	rabbit	0.0002%		some granuloma formation
0.4/4 µm polystyrene latex[30]	rat	4 x 10^{-7} % / 0.0004%		well tolerated
~15 µm ^{99m}Tc human albumin micro-spheres[31]	rat	0.0005%		no reported discomfort
0.1 µm nanodiamonds[32]	rat	0.00052%		no reported discomfort
5 µm DEAE-cellulose fibers[33]	rabbit	0.00053%		no adverse effects
11.6 µm polystyrene microspheres[34]	dog	0.00076%		no reported discomfort
5.4 µm polystyrene microspheres[35]	dog	0.00077%		no reported discomfort
0.7/1/1.5/2.5/3/5 µm spherical silica beads[36]	mouse	0.0012% / 0.0036% / 0.012% / 0.058% / 0.097% / 0.45%		no reported discomfort
3.4 µm polystyrene microspheres[37]	dog	0.0017%		no reported discomfort
7.4 µm polystyrene microspheres[38]	dog	0.0018%		no reported discomfort
0.13 µm gold-silica nanoshells[39]	mouse	0.0018%		all mice remained healthy
2/5 µm bubbles[40]	human	0.002% / 0.004%		well-tolerated
~0.2 µm polymersomes[41]	mouse	0.003%		maximum tolerated dose
1.6 µm hemispherical silica beads[42]	mouse	0.0041%		no reported discomfort
1.6 µm discoidal silica beads[43]	mouse	0.0041%		no reported discomfort
1 µm cylindrical silica beads[44]	mouse	0.0055%		no reported discomfort
0.05-0.18 µm nanodiamonds[45]	rat	0.0059%		no adverse effects
~35 µm macroaggregated albumin[46]	monkey (brain)	0.006%		no behavioral effects
10 µm polystyrene latex[47]	rat	0.007%		focal myocardial degeneration onset
~35 µm macroaggregated albumin[48]	monkey (brain)	0.009%		onset of focal necrosis
0.05-0.18 µm nanodiamonds[49]	monkey	0.011%		no adverse effects
30 µm DEAE-cellulose fibers[50]	rabbit	0.011%		~LD_{50} (acute toxic response)

0.1/1/5/10 µm spheres & 0.1x1x3 µm disks, of polystyrene[51]	mouse	0.012% / 0.12% / 0.61% / 1.2% / 0.033%		no reported discomfort
30 µm albumin microspheres[52]	dog	0.015%		maximum nontoxic dose
	dog	0.025%		evidence of toxicity
	dog	0.19%		pulmonary-artery pressure+300%
	dog	~0.3%		lethal
1-3 µm alumina[53]	rabbit	0.017%		no evidence of disease
40/160 µm DEAE-cellulose microspheres[54]	rabbit	0.018% / 1.13%		no adverse effects
~35 µm macroaggregated albumin[55]	dog	0.02%		tachypnea
~0.2 µm PEG nanoparticles[56]	mouse	0.02%		no reported discomfort
0.5-2 µm SWCNTs[57]	mouse	0.021%		no reported discomfort
3.4 µm polystyrene microspheres[58]	beagle	0.025%		systemic hypotension & myocardial depression
2/6 µm cationic microbubbles[59]	rat	0.026% / 0.071%		minimal hemorrhage
1-3 µm diamond dust[60]	rabbit	0.028%		no evidence of disease
22 µm albumin spheres[61]	dog	0.03%		pulmonary-artery pressure +42%
1-10 µm MWCNTs[62]	mouse	0.037%		no reported discomfort
40 µm starch[63]	human	0.06%		50% nausea and vomiting
7.4/11.6 µm polystyrene microspheres[64]	beagle	0.079% / 0.062%		no significant hemodynamic effect
15.8/48/115 µm polystyrene/latex[65]	dog	0.081% / 0.15% / 0.21%		pulmonary-artery pressure+100%
~0.175 µm PEG-PE liposomes[66]	mouse	0.09%		no reported discomfort
~0.1 µm colloidal carbon[67]	rabbit	0.1%		no reported discomfort
0.557 µm polystyrene latex[68]	rabbit	0.1%		no reported discomfort
40 µm cotton fibers[69]	rat	0.13%		some granuloma formation
74 µm cotton filter paper[70]	dog	0.14%		numerous pulmonary granulomas
1/8 µm carbon[71]	rat	0.2% / 0.2%		no reported discomfort
0.11 µm $Mg_2Al(OH)_6Cl$ "LDH[72]	rat	0.22%		inflammation & some necrosis
0.11 µm $Mg_2Al(OH)_6Cl$ "LDH"[73]	rat	0.66%		lesions, edema & necrosis
3 µm latex[74]	beagle	0.3%		dyspnea
40 µm polystyrene latex[75]	rat	0.4%		~LD_{50}
13.5/90.7 µm latex[76]	mouse	0.21% / 0.46%		24-hr LD_{50}
60-420 µm glass beads[77]	dog	0.25%		~LD_{50}
13.5/90.7 µm latex[78]	rat	0.31% / 0.43%		24-hr LD_{50}
3 µm latex[79]	rat	~1%		est. LD_{50}
0.5 µm *S. aureus* bacteria[80]	mouse	~1%		~LD_{50}
7-8 µm erythrocytes	human	28%-71%		normal range
7-8 µm erythrocytes	human	>71%		polycythemia
7-8 µm erythrocytes	human	85%		likely stroke/heart failure
7-8 µm erythrocytes	human	94%		death from stroke/heart failure

See color codes in Figure 1.

Discussion

Historical data suggests that initial human intravenous tests of microscale diamondoid nanorobots in the 0.5-3 μm size range probably should not exceed a maximum target concentration of Nct ~ 0.001% (e.g., ~13 billion 2-μm spherical nanorobots, of total robot volume V_{robots} ~ 54 mm^3, in an adult human male with V_{blood} ~ 5.4 liters of circulating whole blood), where V_{robots} / V_{blood} = Nct ("nanocrit") is the percentage volume concentration of nanorobots in the blood. Up to Nct ~ 0.005% might still be considered acceptably conservative, given the dashed line in Figure 1 representing the empirical "safe" boundary of D_{sph} (μm) x Nct (%) ≤ 0.01.

The human LD_{50} for freely-circulating microparticles of any kind has not been reported in the literature. Microsphere toxicity in animals due to vascular occlusion is a function of the total volume of microspheres injected.[81] For rats appears to follow a power law of the form $N_{LD50,rat} = M_{body}\ K / D_{sph}^{b}$, where $N_{LD50,rat}$ is the number of spheres intravenously injected to achieve LD_{50} in the rat, M_{body} is rat body weight in kg, D_{sph} = microsphere diameter in microns, and the experimentally-determined constants are K ~ 8.6 x 10^{11} $micron^3$/kg and b ~ 3.15; with a similar relation found for dogs.[82] Simply extrapolating to a human body weight of M_{body} = 70 kg, the LD_{50} whole-body LD_{50} dose of D_{sph} = 1 micron latex microspheres would be $N_{LD50,human}$ ~ 60 trillion spheres, or $Nct_{LD50,human}$ ~ $(\pi/6)\ D_{sph}^3\ N_{LD50,human}$ / V_{blood} ~ 0.6%. This might be considered a pessimistic estimate because the above formula for N_{LD50} is derived mainly from studies of (1) experimental particles that are >10 microns in diameter, whereas proposed bloodborne microscale nanorobots are typically 0.5-3 μm, (2) particles having varying dimensions and atomically rough surfaces, whereas proposed atomically precise nanorobots can have identical radii and atomically smooth and engineered-biocompatible surfaces, and (3) particles that were deployed in animal models (e.g., rats and rabbits) that have smaller average red blood cell diameters than humans. On the other hand, the estimate might be considered optimistic for continuously circulating nanorobots because the aforementioned experimental particles are rapidly cleared from the bloodstream via the liver, spleen, kidney, and lungs, reducing their actual experimental dwell time in the circulation.

It is worth noting that natural erythrocytes, if regarded as superbly engineered biological microscale nanomachines, safely achieve the equivalent of Nct ~ 13% in 8-μm capillaries, Nct ~ 25% in 30-μm pre-capillary channels, Nct ~ 36% in 100-μm arterioles and venules, and Nct = 46% (range 43%-58%) in the largest vessels of the normal human vasculature.[83] This suggests the possibility of at least a 100-1000 fold improvement in the maximum tolerable bloodstream concentration of microscale nanorobots if they are equipped with comparably engineered biocompatible exteriors, as compared to the raw-surfaced and coarsely-shaped passive microparticles surveyed here.

Conclusions

A survey of experimental studies on the pathological effects of intravenous injection of microparticles of various sizes and compositions, conducted over the last 70 years in both animal and human subjects, suggests that initial human intravenous tests of microscale diamondoid nanorobots in the 0.5-3 μm size range should not exceed a maximum bloodstream volumetric concentration of approximately 0.001%.

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