Nanoparticle toxicity and cancer

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Abstract. Nanoparticles (NPs) have provided significant advancements in cancer treatment. But as in any technology, there is a darkside. Experiments have shown NPs in body fluids pose a health risk by causing DNA damage that in of itself may lead to cancer. To avoid the dilemma that NPs are toxic to both cancer cells and DNA alike, the mechanism of NP toxicity must be understood so that the safe use of NPs may go forward. Reactive oxidative species (ROS) of peroxide and hydroxyl radicals damage the DNA by chemical reaction, but require NPs provide energies of about 5 eV not possible by surface effects. Only electromagnetic (EM) radiations beyond ultraviolet (UV) levels may explain the toxicity of NPs. Indeed, experiments show DNA damage from <100 nm NPs mimic the same reaction pathways of conventional sources of ionizing radiation, Hence, it is reasonable to hypothesize that NPs produce their own source of UV radiation, albeit at low intensity. Ionizing radiation from NPs at UV levels is consistent with the theory of QED induced EM radiation. QED stands for quantum electrodynamics. By this theory, fine < 100 nm NPs absorb low frequency thermal energy in the far infrared (FIR) from collisions with the water molecules in body fluids. Since quantum mechanics (QM) precludes NPs from having specific heat, absorbed EM collision energy cannot be conserved by an increase in temperature. But total internal reflection (TIR) momentarily confines the absorbed EM energy within the NP. Conservation proceeds by the creation of QED photons by frequency up-conversion of the absorbed EM energy to the TIR confinement frequency, typically beyond the UV. Subsequently, the QED photons upon scattering from atoms within the NP avoid TIR confinement and leak UV to the surroundings, thereby explaining the remarkable toxicity of NPs. But QED radiation need not be limited to natural or man-made NPs. Extensions suggest UV radiation is produced from biological NPs within the body, e.g., enzyme induced fragmentation of epithelial tissue, exocytosis of small proteins, and ironically, the same molecular markers used to detect cancer itself.

1. Introduction

DNA damage by <100 nm NPs is now [1] considered to mimic the same reaction pathways as conventional sources of ionizing radiation. The most reasonable hypothesis is the NPs are producing their own ionizing radiation at least at UV levels, albeit at low intensity.

NPs producing low level ionizing radiation is consistent with the theory of QED induced EM radiation [2]. By this theory, NPs in body fluids produce at least UV radiation upon absorbing kT energy of colliding water molecules. Even though the UV intensity is low, DNA damage by single strand (SS) and double strand (DS) breaks may occur directly by photolysis of dry DNA or indirectly by forming ROS of peroxide and hydroxyl radicals from the water in body fluids that damage the DNA by chemical reaction.

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Currently, DNA damage is quantified by the oxidative stress paradigm based on the surface area of < 100 nm natural and man-made NPs. However, experimental data [1, 3-13] over the past few decades has placed this paradigm in question because greater DNA damage is found with larger particulate.

The purpose of this paper is to not only explain how QED induced radiations are related to the oxidative stress paradigm based on < 100 nm NPs, but also how larger particulate cause greater DNA damage. But DNA damage need not be limited to natural and man-made NPs. Extensions suggest DNA damage from biological NPs created within the body including enzyme induced fragmentation of submicron epithelial tissue, exocytosis of small proteins, and molecular markers long thought useful in detecting cancer.

2. Background

2.1. EM Energies

EM energies necessary to directly damage the DNA require at least photolysis at UV levels. The DNA ionization potential [3] varies from 7.5 to 10 eV. Breaking SS and DS in dry DNA requires EM radiation [4] having energies above a threshold of 7 eV. The number of DS breaks then increases monotonically to about 12 eV and then remains constant.

The indirect ionizing radiation pathway relies on photolysis to form ROS of hydroxyl and peroxide radicals in the water [5] of the body fluids that cause SS and DS breaks of DNA by chemical reaction. Since QED radiation need only exceed 5.2 eV to break the H-OH bond, the indirect pathway is the more likely DNA damage path.

2.2. Oxidative Stress Paradigm

In the 1990's, evidence that α-quartz particles (Min-U-Sil) having a mean diameter of 5 microns were capable [6] of inducing oxidation damage of biological systems. However, it is likely that some <100 nm NPs were included with the Min-U-Sil particles that actually caused the DNA damage. In silicosis, the induced hemolysis from ROS upon the interaction of silica particles with red blood cell membranes was attributed to the formation of hydrogen peroxide on the particle surface that upon reaction with metal ions by the Fenton reaction produced the hydroxyl radical. Indeed, hydrogen peroxide was detected [7] by ESR in aqueous suspensions of quartz particles. However, the source of hydrogen peroxide that produced the hydroxyl radical has never been conclusively identified.

In 2003, the NP oxidative stress paradigm as a measure of forming ROS was correlated [8] with the surface area of <100 nm NPs, although the mechanism by which the hydroxyl radicals and hydrogen peroxide form was not defined. However, the paradigm was questioned because ESR comparisons [9] of the coarse PM2.3-10 particulate produced a greater number of hydroxyl radicals than the fine PM<2.5 particulate.

Similar problems were found [10] with the oxidative stress paradigm in 2006. Natural and man-made NPs were investigated with regard to the biological consequences of ROS production. Particulate collected from the Los Angeles basin having diameters about 1500 nm and NH_2–PS spheres 1000 nm in diameter showed the clearest evidence of toxicity compared to 100 to 300 nm NPs. Similarly, pulmonary studies were conducted on rats using a wide range of α-quartz NPs that showed [11] about the same toxicity for 10-20 nm synthetic and 300-700 nm (Min-U-Sil) NPs. Nevertheless, DNA damage was attributed to surface activity.

In 2008, DNA damage [12] by silver NPs widely used as bactericidal agents was studied. Bare 25 nm silver NPs while were coated with polysaccharide to an overall diameter of 80 nm. More severe DNA damage comprising DS breaks and apoptosis/cell death was found with the larger coated NPs. Interestingly, otherwise inert gold NPs were found to generate free radicals. Of relevance to QED induced radiation, NPs naturally present [13] in *ex vivo* human skin were found to produce free radicals upon irradiation with VIS (400-700 nm) and NIR (700-1600 nm) light, although VIS and NIR light itself is not ionizing radiation.

2.3. Modified Oxidative Stress Paradigm.

Observations [9-13] suggest the oxidative stress paradigm that correlates DNA damage with the area of <100 nm NPs should be modified to account for the greater DNA damage from larger 300-1400 nm particulate.

But if so, how should the oxidative stress paradigm be modified?

By QED induced EM radiation, the larger particulate do not directly damage the DNA, but rather act to frequency up-convert the FIR inherent in body fluids to higher energy QED photons in the near infrared (NIR). Mie theory [14] shows NPs more efficiently absorb NIR than FIR radiation, and therefore large particulate enhance the UV emission of nearby < 100 nm NPs above that by the FIR alone. Hence, the NP induced oxidative stress paradigm based on <100 nm NPs itself is not modified. Instead, the larger 300-1400 nm particulate are viewed as providing enhancement of the UV radiation from the <100 nm NPs.

2.4. QED Induced Radiations

Ionizing radiation from NPs based on QED induced EM radiation was proposed [2] as an alternative to the high temperatures from heating thought to cause cancer necrosis in photodynamic therapy (PDT). Previously, gold NPs attached to cancer tumours were thought destroyed by high temperatures upon the absorption of NIR laser irradiation. However, conservation of the absorbed laser photon does not proceed by temperature increase of the NP, but rather by the emission of EM radiation at its TIR confinement frequency, typically beyond the UV. By QED theory, the UV radiation causes cancer necrosis – not high temperature.

3. Theory

The DNA may be damaged by NP induced UV radiation by absorbed EM energy from collisions with intra or extra-cellular water molecules. NPs need not enter the cell because the emitted UV radiation readily penetrates the membrane as depicted in figure 1.
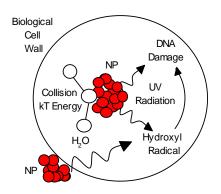

Figure 1. NP emitting UV Radiation and DNA Damage

Intra and extra-cellular water molecules continuously collide with and transfer thermal kT energy to the NPs. Since the water molecules are small compared to the NP, the collisions are inelastic and the transfer of kT energy to the NP is very efficient. The NPs lacking specific heat conserve the collision energy by the emission of EM radiation at the TIR confinement frequency of the NP, usually beyond the UV that is sufficient to produce the ROS that induce DNA damage.

3.1. EM Confinement

QED induced radiation is produced by NPs during the momentary TIR confinement of absorbed EM energy. Although NPs have diameter $D << \lambda$, it is instructive to consider TIR for $D >> \lambda$. The equatorial TIR mode [15] traps absorbed EM energy at the NP surface, the number n of reflections around the QD depends on the wavelength λ of the incident radiation. As $\lambda \to D$, the ratio $\lambda/D \to 2$. The speed of light in the NP is the speed c in the vacuum reduced by its refractive index n_r giving the frequency f,

$$f = \frac{c/n_r}{\lambda} = \frac{c}{2n_r D} \tag{1}$$

NPs having $\lambda >> D$ have the macroscopic index n_r because the speed of light c in a medium is independent of size. QED photon creation in the TIR mode is analog ous with the QM analogy of creating photons of wavelength λ by supplying EM energy to a QM box with walls separated by $\lambda/2$. For the spherical NP as a QM box of diameter D, the Planck energy E induced by TIR confinement at wavelength λ is,

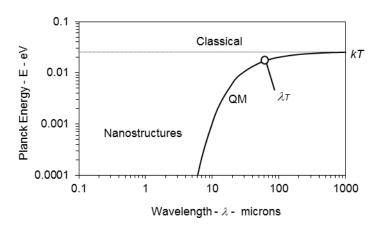$$\lambda = 2n_r D \quad \text{and} \quad E = hf = hc/2n_r D \tag{2}$$

where, h is Planck's constant.

3.2. Classical and QM Oscillators

Classical oscillators by statistical mechanics differ from their QM counterparts. The QM oscillator given by the Einstein-Hopf relation,

$$E = \frac{hc}{\lambda} \bigg/ exp\left(\frac{hc}{\lambda kT}\right) - 1 \tag{3}$$

The average Planck energy E or heat capacity with wavelength λ at $T \sim 300$ K is shown in figure 2.

Figure 2. Harmonic Oscillator at $T \sim 300$ K

Classical oscillators have the same kT energy at all wavelengths λ as shown in figure 2. Hence, the atoms in NPs under TIR confinement have heat capacity to conserve the absorption of EM energy by an increase in temperature.

Submicron QM oscillators lack heat capacity. For $\lambda << \lambda_T = hc/kT$, figure 2 shows that an atom confined in a NP under TIR cannot conserve absorbed EM energy by an increase in temperature. Only for $\lambda > \lambda_T$, does the QM oscillator have the heat capacity of its classical counterpart.

3.3. Vanishing Specific Heat

Classical heat transfer conserves absorbed EM energy by an increase in temperature, but is not applicable to NPs because of QM restrictions on heat capacity under TIR confinement. The specific heat C of a NP may be obtained from the thermal gradient of the average Planck energy E. (equation in the inset of figure 2) depending on the TIR confinement at wavelength $\lambda = 2 n_r D$.
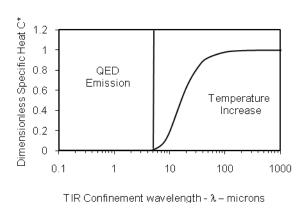
Figure 3. Dimensionless Specific Heat C^*

Differentiating the Einstein-Hopf relation for average Planck energy E with respect to temperature gives the dimensionless specific heat C^*
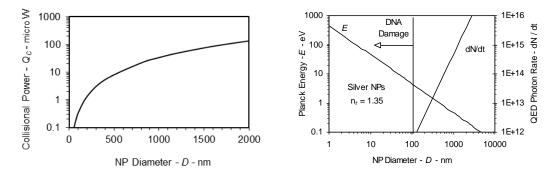
$$C^* = \frac{C}{3Nk} = \frac{\left(\frac{hc}{\lambda kT}\right)^2 exp\left(\frac{hc}{\lambda kT}\right)}{\left[exp\left(\frac{hc}{\lambda kT}\right)-1\right]^2}$$ (4)

where, N is the number of oscillators. At 300K, C^* vanishes for $\lambda = 2n_rD < 4$ microns as shown in figure 3. For $n_r < 2$, the absorbed EM energy for $D > 1$ microns is conserved by a temperature increase while QED emission occurs for $D < 1$ microns.

3.4. Collision Power and QED Induced Photons and Rate

The collision power Q_C of water molecules of mass m transferred to NPs having diameter D is,

$$Q_C = \frac{\pi}{2\sqrt{3}} pPD^2 \sqrt{\frac{kT}{m}}$$ (5)

where, p is the unit probability of full kT energy transfer for inelastic collisions and P is ambient pressure. The mass $m =$ MW/ N_{Avag} where MW = 18 and N_{Avag} is Avagadro's number. The power Q_C with NP diameter D is given in figure 4.

Figure 4. Collisional Power Q_C

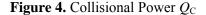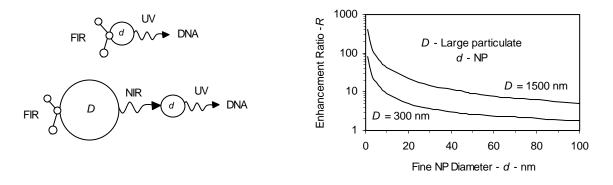**Figure 5.** QED Photons Energy and Rate

Absent an increase in NP temperature, the collision power Q_C is conserved by the emission of QED induced radiation,

$$E\frac{dN}{dt} = Q_C$$ (6)

where, dN/dt is the rate of QED induced photons having Planck energy E created *inside* the NP. For silver having $n_r = 1.35$, the QED induced photon energy and rate is shown in figure 5. Silver NPs <100 nm emit ionizing radiation beyond the UV. Hydroxyl radicals form at 5.2 eV (238 and 123 nm) in $d =$ 88 nm NPs. However, silver NPs > 100 nm emitting non-ionizing radiation in the VIS and NIR lack the Planck energy to produce hydroxyl radicals.

4. Analysis

In QED Induced EM radiation, the oxidative stress paradigm for <100 nm NPs need not be invalidated by the greater DNA damage found in coarse 300-1500 nm particulate, but rather corrected for UV enhancement. Consider an arrangement of NPs of diameter d in relation to larger particulate of diameter D shown in figure 6.

Figure 6. Large Particulate Enhancement

Figure 7. Enhancement Ratio R

Collisions induce the NPs to emit UV and the larger particulate to emit NIR radiation,

$$Q_{UV} = \frac{\pi}{2\sqrt{3}} pPd^2 \sqrt{\frac{kT}{m}} \text{ and } Q_{NIR} = \frac{\pi}{2\sqrt{3}} pPD^2 \sqrt{\frac{kT}{m}} \tag{7}$$

Mie theory [14] gives the absorption efficiency Q_{abs} of the NPs to the NIR radiation,

$$Q_{abs} = F\left(\frac{d}{\lambda_{NIR}}\right) \text{ and } F = \frac{24\pi ab}{\left(a^2 + b^2 + 2\right)^2 + 4a^2b^2} \tag{8}$$

The NIR wavelength $\lambda_{NIR} = 2n_rD$. Parameters a, b are the real and complex refractive indices of the NPs. The DNA absorb power Q_{UV+NIR},

$$Q_{UV+NIR} = Q_{UV} + Q_{abs}Q_{NIR} \rightarrow R = \frac{Q_{UV+NIR}}{Q_{UV}} = \left(\frac{D}{d}\right)\frac{F}{2n_r} + 1 \tag{9}$$

The UV enhancement ratio R for silver NPs having $a = 1.35$ and $b = 4$ by larger silica particulate having $n_r = 1.45$ is shown in figure 7. For 300 and 1500 nm particulate, DNA damage by silver NP induced hydroxyl radical at 5.2 eV occurs at $d = 88$ is shown enhanced by ratios R of about 2 and 8, respectively.

5. Discussion
The oxidative stress paradigm that claims the ROS correlate with the area of <100 nm NPs is not modified because of the greater DNA damage found with the larger 300-1500 nm particulate. The larger particulate themselves do not damage the DNA, but rather enhance the DNA damage caused by the <100 nm NPs.

5.1. Similarity of NP induced UV to Conventional Radiation
Air pollution [8, 9] studies give direct evidence of DNA damage by PM10 having < 50% by mass of combustion derived nanoparticles (CDNPs). The CDNPs are carbon centered NPs from automobile exhausts, but NP induced DNA damage mechanisms are currently not known.

QED induced radiation is produced in NPs at least at UV levels from which molecular mechanisms for DNA damage may be formulated. Indeed, NP induced respiratory DNA damage mimics [1] that by ionizing radiation, albeit at lower UV intensities. This means DNA damage mechanisms under ionizing radiation are applicable to NP induced DNA damage.

5.2. Oxidative Stress Paradigm

Recent pulmonary studies on rats [11] contradict the NP oxidative stress paradigm that states DNA damage is caused by toxicity that correlates with the surface area of <100 nm NPs. Indeed, the toxicity of 500 nm mined α-quartz (Min-U-Sil) particles was found equivalent to that from synthetic 12 nm quartz NPs. The haemolytic potential of α-quartz in red blood cells was attributed to the surface activity [6] caused by defects, and jagged edges in producing ROS. Silica is known to generate hydroxyl ions from hydrogen peroxide, and indeed both have been detected aqueous suspensions α-quartz. However, the specific reactions leading to the formations of hydrogen peroxide from silica have never been identified.

In contrast, QED induced EM radiation from <100 nm NPs unequivocally provides the UV to directly form the hydroxyl radicals and hydrogen peroxide. Surface activity itself has nothing to do with ROS produced by α-quartz.

5.3. Anti-Microbial Silver Nanoparticles

Silver NPs having the greatest degree of commercialization are of interest in DNA damage because of the potential treatment of inflammations in the blood. Indeed, the antimicrobial activity in controlling infections [16] and limiting bacterial growth [17] in the food industry are only a few of the many applications of silver NPs.

However, silver NPs also damage [12] the DNA. The ROS including hydroxyl radicals and hydrogen peroxide are thought produced by surface chemistry. But surface chemistry cannot be the mechanism for bactericidal action of silver NPs because polysaccharide coated silver NPs produced greater DNA damage than for bare silver NPs. EM energy is required to produce ROS that cannot be produced by surface chemistry. But QED induced EM radiation is produced in NPs beyond the UV. Indeed, the 3-fold increase in the diameter of the coated to bare NPs corresponding to EM confinement wavelengths from 68 to 200 nm suggest the NPs exposed the DNA to UV beyond 6.2 eV. To avoid DNA damage, NPs larger than 100 nm are required, but this would negate the bactericidal action of the silver NPs.

5.4. Sunscreens

The interaction of sunlight with the human skin has led to a fragile equilibrium between the EM radiation necessary for life and UV levels that damage the DNA. Prompted by the nearly epidemic increase in skin cancers over the past few decades, the European Commission has lowered the acceptable ratio UVA/UVB. Here UVA (320-400 nm) and UVB (280-320 nm). However, only about 6 % of sunlight is in the UV with 52% in the VIS and 42% in the NIR suggesting the VIS and NIR0 are somehow also producing DNA damage.

Indeed, the ROS in the form of free radicals were found [13] in human skin under both UV and VIS/NIR radiation. UVB is ionizing radiation that is expected to produce free radicals, but the VIS/NIR is not. The free radicals measured were thought caused by heat from the VIS/NIR increasing the skin temperature. But there is no known mechanism by which simply raising the temperature produces free radicals.

QED induced EM radiation at UV levels produces ionizing radiation provided <100 nm NPs are present on the skin surface. Adherent sub cutis and fascia were removed, but the concentration of the remaining natural NPs was not given to assess QED induced EM radiation in producing free radicals directly from the NPs by VIS/NIR radiation *Ibid*. Nevertheless, it is highly likely NPs were in fact present to explain the free radicals observed.

Sunscreens use white color zinc oxide particles to deflect damaging UV radiation, but the zinc oxide may be made transparent and more absorbent by shrinking the particles down to <100 nm NPs. By QED induced EM radiation, the zinc oxide NPs absorb fractions of the VIS/NIR radiation only to produce higher energy UV radiation that damages the DNA. To avoid DNA damage, NPs > 100 nm would convert the UV content in sunlight to non-damaging VIS/NIR radiation. The claim that NPs are absorbed in the skin and therefore cannot cause DNA damage to the brain or liver do not consider the UV radiation to penetrate the skin and induce DNA damage in the RBC.

5.5. Cancer Therapy

In PDT, photosensitizers in the form of NPs that preferentially attach to cancer cells and activated by NIR radiation are claimed [19] to produce singlet oxygen, thereby destroying the cells by chemical reaction. But cancer cells are destroyed without photosensitizers, thereby begging the question of what actually caused cancer necrosis in PDT.

Prior to photosensitizers, high temperature was thought to induce cancer necrosis in PDT. But NPs lack the specific heat [15] to allow a temperature increase to conserve the absorbed NIR radiation, and therefore QED induces the NP to emit EM radiation beyond the UV that causes cell necrosis, thereby obviating the need for photosensitizers in PDT to activate the oxygen singlet state.

Whether DNA is not damaged by a certain frequency range of ionizing radiation that is damaging to a specific cancer is an unlikely conjecture. But if research shows otherwise, the selection of a NP size tuned solely to the frequency causing necrosis of the cancer may be possible. Only then may NPs be justified in cancer therapy.

6. Extensions to Biological NPs

Cancer research is only beginning to recognize the remarkable fact that natural and man-made NPs in body fluids emit low-level UV radiation. But UV is also emitted from biological NPs < 100 nm having a refractive index greater than the water surroundings. For cancer cells, the index varies from 1.34 to 1.38 compared to 1.33 for water. Only the process by which the biological NPs form differs, a brief description of which is as follows.

6.1. Disorganization o f Epithelial Tissue

Epithelial tissue forming the outer layers of the skin protect exterior surfaces of the body, but also provide protection for hollow organs and glands including the breast, prostate, colon, and lung from body fluids. Epithelial tissue is organized by a submicron thick < 100 nm basement membrane (BM) that provides the structural scaffold template for the extracellular matrix (ECM). Breakdown of the BM is associated with the spread of tumors.

Loss of integrity in the ECM is triggered [19] by enzymes called matrix metalloproteinases (MMPs). Indeed, MMPs induce the epithelial-mesenchymal transition (EMT) that fragment the BM and move through the body. In breast cancer, EMT allows tumor cells more mobility to penetrate barriers like the walls of lymph and blood vessels, facilitating metastasis, e.g., the MMP-3 enzyme causes normal cells to produce a protein called Rac1b that is found only in cancers.

Current thought is the Rac1b protein found in most cancers itself damages the DNA. Contrarily, the ROS are not induced by Rac1b to stimulate the development of cancer by mutation of genomic DNA. Rather, the ROS are formed in a side reaction from the QED radiation emitted from the NPs of fragmented BM. Nevertheless, the Rac1b is still a NP that emits UV and can damage DNA.

6.2. Exocytosis of Small Proteins

The exocytosis or release of fusion products into the extracellular fluid through the tumor cell membrane is known [20] to produce onco proteins. Indeed, the release of fusion products is required for the initiation and growth of malignancy. It should come as no surprise that exocytosis is linked to tumor growth. Hence, QED induced radiation at UV levels from submicron fusion products as biological NPs during exocytosis is consistent with malignancy.

6.3. Molecular Markers in Cancer Detection

Changes that occur in cancer cells compared with normal tissue can be detected in body fluids and used as molecular markers of cancer. As an epithelial tumor grows, cancer cells fragment from the organ epithelium and enter the body fluid as NPs making it possible to detect molecular markers such as DNA mutations.

Protein markers are of interest in QED induced radiation whether by BM fragmentation or exocytosis because the UV radiation produced is damaging to DNA. One such marker is the telomerase enzyme [21] expressed by almost every cancer type: head and neck, lung, breast, colon, pancreas, bladder, and prostate cancers.

7. Summary

- NPs < 100 nm produce QED induced radiations beyond the UV that damages DNA.
- NIR lasers used to activate NPs of photosensitizers are not necessary to produce UV radiation. The thermal *kT* energy of water molecules that collide with the NPs upon absorption is induced by QED to be frequency up-converted to UV levels.
- QED only induces ionizing radiation beyond the UV at NP diameters <100 nm.
- QED radiations cause the large 300-1500 NPs to produce VIS/NIR radiation that enhances the UV emission from adjacent <100 nm NPs.
- The NP induced oxidative stress paradigm that DNA damage is caused by ROS produced proportional to the area of <100 nm NPs needs to be modified to include the enhancement by the larger 300-1500 nm particulate.
- Surface activity of <100 nm NPs has nothing to do with NP toxicity.
- Sunscreens having NPs < 100 nm NPs should be banned in favor of NPs > 100 nm that would absorb UV radiation that then is frequency down-converted to DNA non-damaging VIS and NIR radiation.
- The widespread use of silver NPs in limiting bacteria in food processing increases the risk of developing cancers.
- MMP-3 disintegration of BM produces submicron biological NPs that produce low-level sources of UV radiation that readily move throughout the body.
- Submicron cancer markers are themselves a source of UV radiations.
- More study directed to DNA damage from the UV radiation produced by NPs is suggested to extend the preliminary assessment given in this paper.

8. Conclusions

QED radiation is proposed as the mechanism by which DNA is damaged by low–level UV emission from natural, man-made, and biological NPs, the DNA damage by NPs mimicking the same reaction pathways of conventional ionizing radiation. Specifically,

- The DNA damage induced by NPs is a cancer risk if not properly repaired. Given that NPs produce ionizing radiation beyond UV levels from the QED induced collision energy of water molecules, and that natural, man-made, and biological NPs are ubiquitous, the *conjecture* may be made that NPs are one of the most likely cause of cancers in man.
- The sensitivity of DNA to ionizing UV radiation should be determined to see if cancer necrosis is possible without causing DNA damage.

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