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The key to maximizing the benefits of antimicrobial and self-cleaning coatings is to fully determine their risks
Han Fu and Kimberly A Gray

Antimicrobial and self-cleaning nanomaterial coatings have attracted significant research attention in recent years due to the growing global threat of infectious diseases, the emergence of new diseases such as COVID-19, and increases in healthcare-associated infections. Although there are many reportedly successful coating technologies, the evaluation of antimicrobial performance is primarily conducted under simple laboratory conditions without adequate testing under real environmental conditions that reflect practical use and more importantly, reveal unintended outcomes. Furthermore, there is no standardized evaluation methodology to assess the long-term stability or the consequences associated with coating deterioration, such as the ecological impacts of nanomaterials or the proliferation of antibiotic-resistant bacteria/genes. In this review, we propose a precautionary framework that integrates a rigorous assessment of potential risks and limitations of nanomaterial coatings for antimicrobial applications as intrinsic to a comprehensive evaluation of their benefits. In addition, we summarize some emerging coating technologies as promising strategies to minimize unintended risks and enhance performance.

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Introduction
According to the World Health Organization, infectious diseases kill more than 17 million people annually and in the last 20 years over 30 new diseases, including COVID-19, have emerged [1a]. Globally, the proliferation of infectious diseases, many of which are zoonotic, is attributed to a myriad of factors such as a rapidly changing climate and shifting biomes, deforestation, urbanization, global air travel, lack of preparedness, and so on [1b]. Locally, nosocomial infections or healthcare-associated infections (HAI) are a major cause of patient morbidity and mortality, occurring in all kinds of healthcare settings via direct and indirect routes, including pathogen transmissions among patients and healthcare workers (airborne and direct contact), postoperative complication, and contact with contaminated surfaces [1c]. Among the many routes of transmission, control of pathogens through the creation of biocidal and self-cleaning, high touch surfaces is a burgeoning area of research and development.

The COVID-19 pandemic has brought the struggle of protecting public health from a raging contagion into sharp focus. Most fatalities associated with previous pandemics (e.g. 1918 and 2009 H1N1 inuenzas), however, were due to bacterial or fungal co-infection [2] and similar findings are emerging with COVID-19 [3]. Co-infections may be pre-existing conditions or may be transmitted nosocomially (e.g. hospital-acquired pneumonia caused by Streptococcus pneumoniae or many other bacteria). In general, cleaning practices in any emergency care or clinical setting can be erratic and intermittent, and high touch surfaces, such as instrument touchscreens and control panels, are particular sites of bioburden accumulation that may present direct and indirect health risks to COVID patients, immunocompromised individuals, medical staff and the general public in and out of hospitals.

Although not the dominant mode of exposure, there is evidence that SARS-CoV-2 and many other pathogens can stay viable on high-touch surfaces for hours to days [4]. Coating technologies based on the unique properties of engineered nanomaterials (ENMs) offer special opportunities to tailor surfaces to inactivate pathogens and to be self-cleaning [5**,6]. Yet, in the urgent rush to find pathogen control methods, a knowledge gap emerges between laboratory results and the longer-term performance of ENM coated products, especially as it relates to unintended environmental consequences. In this review, we present a precautionary framework that investigates and integrates the inadvertent risks of ENM coatings for biocidal and self-cleaning applications with public and commercial benefits over the product life cycle. We also present some novel advanced coating materials and technologies that highlight this approach.

A precautionary framework: a comprehensive approach to evaluating ENM coatings as biocidal and self-cleaning surfaces
Benefit-risk assessments are commonly used in the pharmaceutical sector. Unlike other ordinary consumer
products, pharmaceutical products require multiple stages of clinical testing to collect sufficient data to evaluate the efficacy, manufacturing quality, acute safety, chronic risks, and management of those risks before final approval [7,8]. The U.S. Food and Drug Administration (FDA) has established a standardized benefit-risk framework to structure and manage the benefits (efficacy of the products) and risks (potential harm and uncertainties) that determine final product approval. We revise this framework to develop a precautionary approach that stresses the need to fully identify unintended risks, as well as targeted benefits over a product’s life cycle with careful attention to post-use fate.

Table 1 illustrates how we adapt the FDA framework to ENM coatings and explains four decision factors for which evidence and uncertainties are evaluated to support commercialization [8]. The first factor, analysis of condition, recommends going beyond the assessment of targeted pathogens to include those associated with HAI and other co-infections. The second factor, current treatment options, entails a thorough inventory of the existing technologies and their deficiencies to direct the design of new coating materials. The next two considerations highlight benefit-risk and precautionary concepts: benefits need to be evaluated from antimicrobial performance tests in the lab and under field conditions, and risks encompass deliberate consideration of potential short-term and long-term adverse outcomes associated with direct exposure to ENM-coated product or indirect exposure to ENMs detached from coating surface. Risk management determines if risks can be contained during the life cycle and afterlife of the materials and products. For each decision factor, data are required to provide action, all of which is then assessed to determine if designs need to be modified or if products can move to the next stage of commercialization.

Evaluating benefits: a standardized field-testing system involving relevant environmental conditions

Since the 1980s, professional organizations, such as the International Organization for Standardization (ISO) and American Society for Testing and Materials (ASTM), have developed various antimicrobial testing protocols that probe the growth and survival of microbes under standard conditions. For example, ISO 22196 measures the antibacterial activity on plastics and other non-porous surfaces (https://www.iso.org/standard/54431.html); ISO 27447 provides the testing method for antibacterial activity of semiconducting photocatalytic materials (https://www.iso.org/standard/69874.html); ISO 21702:201 provides the measurement of antiviral activity on plastics and other non-porous surfaces (https://www.iso.org/standard/71365.html); ASTM E2180 quantifies antimicrobial agent performance in polymeric materials such as textiles (https://www.astm.org/Standards/E2180); ASTM E2149 tests the antimicrobial activity under dynamic contact conditions (https://www.astm.org/Standards/E2149.html). Many research teams and manufacturers conduct at least one of these testing protocols.

| Table 1 |
| --- |
| **A modified benefit-risk framework for nanomaterial-coated products (adopted from the FDA framework found at [https://www.fda.gov/files/about%20fda/published/Benefit-Risk-Assessment-in-Drug-Regulatory-Decision-Making.pdf](https://www.fda.gov/files/about%20fda/published/Benefit-Risk-Assessment-in-Drug-Regulatory-Decision-Making.pdf))** |
| Decision factor | Action |
| Analysis of condition | Describe the severity of the issue:  
• What are the target pathogens?  
• What are other HAI or co-infection target pathogens?  
• How dangerous are those targets (their biohazard levels)? |
| Current treatment options | Describe the current biocidal and self-cleaning technologies in the market:  
• How well do the current technologies meet clinical needs?  
• Is there an urgent unmet need for new coating technologies? |
| Benefits | Characterize and assess the benefits:  
• What are the mechanisms of pathogen control?  
• How is self-cleaning performance engineered into the product?  
• What is the antimicrobial efficiency of the proposed ENM-coating technology under real performance conditions?  
• What is the competitiveness of the proposed technologies in the market? |
| Risks and risk management | Characterize and access safety concerns and their management:  
• What are the potential adverse effects of ENMs on non-target organisms and humans?  
• What are the risks of antibiotic resistance activation during the lifetime of the products and post-use?  
• How severe are those adverse effects in short term versus long term?  
• How can those risks be managed during the life cycle of the products and post-use? |
and provide test results as the ‘quality certification’ of their ENM-coated products.

The existing methods, however, test microbial growth in synthetic media, using pure cultures, and with direct contact between a model microbe and the coated surface. Such constraints do not reflect the complicated environments of practical application. Environmental conditions influence the bioactivities of microorganisms, change the bio-physico-chemical properties of coatings, and disrupt interactions between the target pathogens and the coated surface. Therefore, the performance of existing testing methods represents ‘preliminary results’ for benefit evaluation; there is a critical need to develop a ‘standardized’ field-testing system that captures more faithfully possible or probable environmental conditions. Table 2 summarizes the critical environmental conditions which should be evaluated in a field-testing system.

Since there are so many parameters and possible mechanisms of action, screening the efficacy of antimicrobial materials has been largely conducted on a material-by-material basis. In the pharmaceutical industry, however, quantitative structure-activity relationships (QSAR) are used to screen potential drug models. A similar approach could be developed for screening ENMs for various mechanisms of microbial inactivation. Although the exact antibacterial mechanisms of ENMs are poorly understood, there are multiple, simultaneous modes of action and ENMs are increasingly employed to target bacteria in medical interventions as alternatives to antibiotics [9]. The compilation of such a database would deepen our insight into the relationship between the biocidal performance and several key elements including the ENM properties, the targeted pathogen properties, the environmental factors, and even the manufacturing costs. Such information would save substantial time and resources at the design and development stage. A major challenge, however, is associated with the nearly infinite structural and functional possibilities that functionalizing ENMs or creating nanocomposite materials offer. At the same time, quantitative ENM structure-biocidal activity relationship

| Table 2 |
|---|
| **Recommended environmental factors for evaluation in field-performance tests** |
| Environmental conditions | Description | Reference |
| Transmission routes | Microbial transfer to the coated surface via different routes: direct dry touch, direct wet touch, aerosols, airborne particle deposition, and so on. Different transmission routes affect the interaction between microorganisms and the coated surface, such as contact area, surface chemistry, charge, wettability, and morphology of the microorganisms. | [10,11] |
| Contact time | Depending on the application, the contact between a coated surface and microorganisms may be static (e.g. door handle) and/or dynamic (e.g. face mask or a continuous flow system). Insufficient contact time between microbes and the surface diminishes inactivation efficiency and increases the risk of microbial colonization of the surface and hence, altered surface properties. | [12] |
| Microbial community | In the natural environment, microorganisms live in communities, such as biofilms. Biofilms contain a variety of bacterial, fungal, algal species encased in a protective matrix of extracellular polymeric substances. In response to harsh conditions and chemical exposure, biofilms can harbor bacteria with antibiotic resistance and serve as reservoirs of resistance genes. | [13] |
| Biological fluids | Human contact with coated surfaces may deposit biological fluids such as blood, saliva, saline, and urine. These fluids may contain microbes, ions, proteins, enzymes, blood plasma and cells, which can change the properties of coatings (such as pH, surface roughness, wettability), disrupt the inactivation of target pathogens, and induce biofilm formation. | [14,15] |
| Chemicals | At clinical sites, periodic cleaning (using sanitizers/detergents) on high-touch surfaces is required. Although sanitizers/detergents are also biocidal agents, possible damage to the coatings by chemicals should be investigated. | [16,17] |
| Temperature/Humidity | Since the coated products function in an indoor environment, temperature and humidity are two important environmental factors. Temperature/humidity may modify the reaction kinetics of biocidal agents or suppress the interaction between microbes and biocide agents. Also, bioactivities and growth rates of pathogens vary at different temperature and humidity levels. | [18–20] |
| Dust | Dust has a complex composition containing both active and inert components. The active components, such as microbes, can have a competitive relationship with target pathogens on coated surfaces; at the same time, the inert components, such as fine sand and minerals, dander and glass fibers, can block the contact area on the antimicrobial surface or cause physical damage. | [21] |
| Light | Light and exposure time play an important role for photoactive ENMs-coated surfaces (TiO2, Fe2O3, ZnO and CuO). The spectral properties of the light source (intensity and wavelength) directly affect the generation of reactive oxygen species (ROS) and reaction kinetics influencing antimicrobial performance. Also, there are some stability concerns with photocatalyst-coated surfaces under illumination: ROS generated via light may damage the substrate (such as cotton and other carbon-based polymeric materials) and cause ENM detachment. | [22,23] |
| Lifetime | Over long-term operation, mechanical damage, chemical oxidation, surface detachment and surface conditioning have been reported to cause coating deterioration. Also, more environmental risks are associated with aged and malfunctioning coated products such as unexpected ENM detachment and activation of antibiotic resistance. | [24,25] |
models would be of great value in identifying potential, unintended ecological and human health risks.

Evaluating the unintended environmental risks of nanomaterials

With the dramatic market expansion of ENM-based products over the last 20 years, the global impact of nanoparticles on the environment and human health is a growing concern for which risk assessment and management have not kept pace. The National Research Council (NRC) long ago published a standard approach to assess and manage the potential environmental and health impacts associated with environmental exposures to chemicals (Figure 1a) and ENM-coated products should be similarly assessed [26].

Risk assessment

The NRC framework evaluates risk in four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. Unfortunately, for ENM-coated products, data collection is limited primarily to the first three steps. A major question for ENM coatings is how to accurately determine dose-response relationships. The properties and performance of ENM-coated products are a function of ENM surface coverage, surface area, coating thickness and ENMs detachment rate/amount. In addition, the performance of detached ENMs is highly related to their surface area per unit mass or volume, rather than mass concentration. Most research focuses on the acute cytotoxicity of a single suspended ENM particle to a single microbial population over relatively high, albeit measurable, dose ranges [27**]. Yet, given the widespread use of all ENMs, their release into the environment, either with use or disposal, creates ENM mixtures. Interactions among ENMs may induce self-assembly to form new types of ENMs having chemical/physical properties (additive, antagonistic or synergistic) that differ from the parent materials. Additionally, several environmental parameters affect ENM toxicity, such as light, natural organic materials, and common ions [27**]. Release of ENMs (whether they are suspended or coated on different substrates) and their morphologies (e.g. nanotubes, nanorods, and nanosheets) also affect their interactions with dother ENMs/microbes and responses to different environmental parameters. More detailed and comprehensive studies are needed to understand the ecological effects of ENM release, their morphologies, and ENM mixtures under environmental conditions in order to adequately detail precautions that will control ENM release.

Another associated environmental hazard of ENMs or ENM-coated products is the spread of antimicrobial resistance, which is a critical medical challenge in the healthcare system (e.g. silver-resistant bacteria can be found commoly at hospitals and in their wastewater effluents [28]). Antimicrobial resistance can arise either because of chromosomal mutations in bacterial cells or the acquisition of an extrinsic resistant gene from other cells (horizontal gene transfer). This risk increases when the exposure of antimicrobial agents remains at low, sublethal concentrations over long times. Since the biocidal action of ENMs likely involves multiple, simultaneous interactions (oxidative and non-oxidative stress, metal ion release) with microbes, it is unlikely for them to develop ENM resistance, but ENMs may facilitate the horizontal transfer of antibiotic-resistant genes in a variety of ways [9]. A deeper investigation is needed to understand specific effects on transformation, transduction or conjugation mechanisms of horizontal gene transfer in pathogenic bacteria and to probe ENM effects on cell permeability, reactions with cellular proteins and lips, and sublethal effects on metabolic functions.

Although a few researchers have interrogated the cytotoxicity of ENMs in mammalian cells with in vitro studies, there exists a debate on the toxicity of ENMs to human. Empirical evidence shows correlations between the use of ENM-containing products and tissue inflammation and/or apoptosis [29]. There are many observations such as ENM co-location with tumors or their impact on the immune system, that we can not explain mechanistically or predictively [30]. Research is required to elucidate the dose effects of acute and chronic exposure to ENMs and the variable effects related to exposure pathways such as dermal contact, inhalation, and ingestion.

Risk management

In addition to comprehensive risk characterizations, several other factors affect the formulation of a final risk management plan: existing regulations, possible control strategies and related economic and social considerations. A suitable plan needs to be based on continued data collection through the life cycle of the ENM-coated products. Figure 1b summarizes the collection of necessary data to formulate control strategies for risk management.

In recent years, several specialized frameworks, which include diversified targets, assumptions, regulation considerations and discussion criteria, have been developed based on the same NRC paradigm [31]. For example, the DF4nanoGrouping framework concentrates on human health hazards and the NanoREG framework is aimed at providing a quick screening which uses the physical/chemical properties of ENMs to estimate the potential environmental risks [32]. It is also worth mentioning that some EU-funded projects, such as SUN (www.sun-fp7.eu) and GUIDENano (www.guidenano.eu) are developing web-based risk assessment tools for ENMs in industrial use and along their life cycle. Overall, comprehensive risk evaluation remains challenging because of insufficient data collection and reporting to complete the determination of risk assessment and risk management. In the U.
S. although the life cycle assessment of some ENMs has been well studied (e.g., nano-sized silver [33]), there is no federal or state legislation specific to ENMs. Under the Toxic Substances Control Act (TSCA), ENMs are regarded as chemical substances and since 2017 reporting and recordkeeping information is required for new and some existing ENMs. Many scientists believe, however, that EPA’s chemical risk evaluations under TSCA are inadequate and will remain that way until the best scientific practices are integrated into the risk evaluation and systemic review process. In the EU, ENMs fall into the general ‘substance’ category under REACH, the
overarching legislation applicable to material manufacture, commercialization and use. Since 2020, explicit reporting requirements have been expanded within REACH for ENMs to include chemical safety assessments and downstream use obligations.

Risk management requires a global effort by all parties involved over the life cycle of the products, such as the initial designers/developers in the laboratory, the manufacturers and distributors, the end-users, the waste collectors, the research teams who study/monitor the environmental hazards, the environmental and health institutions, and the regulatory institutions. Several EU-funded projects, such as NANOReg, EU Nanosafety Cluster, NanoMILE and NanoSolutions, are attempting to coordinate data from a number of partner institutes and establish a harmonized data infrastructure tracking the environmental safety assessment of ENMs [32].

Emerging coating technologies: how to maximize benefits and minimize risks
There are three primary approaches employed in developing conventional antibacterial coatings:

- **Biocide release:** Active biocidal agents (such as metal ions and radical oxygen species) are released from or generated by ENM-coated surfaces to inactivate pathogens. Examples include nano-silver, nano-zinc/zinc oxide, and nano-TiO₂.
- **Contact killing:** After direct contact, inhibition of microbes is achieved via cell membrane damage, DNA damage, enzyme deactivation and other genotoxicities. Examples include chitosan and other polymeric coatings [34], nano-silver, nano-TiO₂ [35] and nano-copper/copper oxide.
- **Anti-adhesion:** The surface topography and wettability are modified to repel microbe attachments and further inhibit the formation of biofilms.

Nano-silver, nano-copper/nano-copper oxide, and titania-coated surfaces, which are based on biocide release/contact killing mechanisms, dominate the market [5**]. Yet, there are several deficiencies in these traditional technologies, which need to be highlighted in the risk evaluation: 1.) The amount of biocidal agent is finite and the reaction kinetics may diminish over the long term, which may result in a decrease in antibacterial efficacy and formation of biofilms; 2.) Surface damage and nanomaterial detachment may occur leading to the deterioration of the antimicrobial surface and promotion of environmental risks.

The current development of ENM-coated products emphasizes several novel features, which can overcome those deficiencies and maximize the benefit/risk ratio by a.) increasing the antimicrobial or biocidal efficiency; b.) enhancing the biocidal durability; c.) augmenting the physical/chemical stability; d.) improving biocompatibility; e.) avoiding induction of antibiotic resistance. We summarize some emerging technologies (Figure 2) aimed at incorporating these features into their coatings:

**Technology 1: Biomimetic anti-adhesion coating**
Pathogenic bacteria-repellent or omniphobic anti-adhesion coatings have become very popular in recent years. These repellent surfaces can permanently prevent bacterial colonization and biofilm formation. They are inspired by the skin textures of aquatic organisms such as sharks and sea stars, which are exposed to microbes but rarely show biofouling. Scientists engineer surface topography at the micro-/nano-scale to mimic the skin of those aquatic organisms [36*,37,38].

**Technology 2: Controlled release coating**
A multiple-layer deposition strategy is applied to control the rate of biocide release. A capping and protective layer that is biocide permeable is deposited over an ENM-coated layer [39,40].

**Technology 3: Plasma-based surface coating**
Plasma techniques provide a novel coating method to deposit charged antimicrobial particles, such as ions/electrons/ radicals, on the surface of the substrate. In addition, antimicrobial particles can be implanted into the substrate at controlled depths. Deposited/implanted ENMs show greater stability than traditional ENM coatings [41*,42].

**Technology 4: Multi-functional coating**
To enhance the antimicrobial efficiency, durability, and surface stability, one strategy is to design coatings that incorporate numerous antimicrobial mechanisms such as multiple biocide-releasing ENMs [43,44], the combination of biocide release and contact killing ENM-coatings [45], and the combination of contact killing and anti-adhesion coatings [46]. Another research direction is to combine the traditional antibacterial materials with other novel materials that are microbially inert but corrosion-resistant, self-healing, or capable of improving physical stability [47,48].

**Technology 5: Kill-release switchable surface coating**
One challenge of the biocide release/contact killing strategy is that dead cells may accumulate on the coated surface, which may prevent the contact of other microorganisms, modify the surface properties of the coating, and induce the formation of biofilms. One novel strategy is to design a kill-then-release surface with the switch between the kill-mode and release-mode controlled by certain stimulating signals such as temperature, pH, wetness, salinity, and so on [49**,50**].
Concluding remarks
In this review, we propose a precautionary framework based on more comprehensive estimates of the benefits and risks over the life cycle of ENM-coated products. Undoubtedly the rapid development of ENM-coating technologies helps to prevent the spread of infectious diseases and improve the quality of life. Yet, there may be some ENM coatings that fail to perform as they were designed over extended use and even more seriously, promote unintended and deleterious impacts to human and ecological health. In order to minimize the risks and maximize the benefits of long-lasting biocidal and self-cleaning performance, ENM-coated products should undergo standardized field-testing, the results of which can be continuously incorporated into predictive models of ENM interactions and behavior under defined conditions. Serious consideration and study of the unintended environmental impacts of ENMs on the microbial and human cells is key to a precautionary evaluation framework. Finally, it is imperative to monitor risks over the entire life cycle of ENM-coated products and generate reliable risk management plans. With this knowledge, ENM design can be modified to minimize or even prevent unfavorable outcomes.

Conflict of interest statement
Nothing declared.

Declaration of Competing Interest
The authors report no declarations of interest.

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Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- - of outstanding interest

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In this review, the authors identify the knowledge gap between the laboratory studies and the ecological effects of the metal-based engineered nanomaterials (ENMs) in real environments: the studies of ENMs under controlled laboratory environments cannot present the behavior of ENMs in real environments. The authors discuss the future research directions to bridge this gap, which entails the ecological effects of mixtures of ENMs, the long-term environmental exposure, the effect of complex environmental conditions, and the effects on different microbial systems.

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