Concern-Driven Approach to Human Health Risk Assessment of Nanomaterials: A Nanoparticle Screening Assessment Framework

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SUMMARY

The Canada-US Regulatory Cooperation Council (RCC) was created in 2011 to increase regulatory transparency and coordination between Canada and the US in several areas [1]. Based on the analysis and discussions that occurred during the Canada-US RCC, a common approach for assessing and identifying additional testing requirements for nanoparticles was developed, based on current knowledge of particle toxicology. This common approach/framework is presented here, and represents an effort to systematically focus human health concerns and additional testing requirements for nanoparticles based on physical characteristics (i.e. particle shape, aspect ratio, particle/fibre size, solubility, composition and surface chemistry).

Keywords: human health, risk assessment, nanoparticle, nanotoxicology.

1 OVERVIEW

Particle toxicology is different from molecular toxicology in that the *physical characteristics* of the particles are most often the primary drivers of toxicity rather than their composition alone. Consequently, different paradigms are required in particle risk assessment than in molecular risk assessment.

Particles come in various shapes, sizes and composition. Nanoparticles are currently identified by nomenclature methodology based primarily on chemical composition (chemical name and CAS RN). However, one chemical name and/or CAS RN may represent a wide array of substances with the same composition but with varied physical-chemical characteristics (i.e., particle size distribution, shape, surface chemistry). Technological advances now allow the manipulation of matter at the nanometric scale, resulting in the creation of novel substances with characteristics not always easily predicted from current knowledge on bulk-size chemicals. A substance with a fixed composition can now be engineered into many different shapes (e.g. spheres, fibres, sheets) with varying physical characteristics (e.g. size, crystal structure, surface charge). Although these different forms possess identical composition, the effects of changing the physical parameters may alter the substance's behaviour in environmental and biological media, thereby influencing its toxicological properties. The magnitude and specificity of this influence are currently impossible to predict in the absence of nanoparticle-specific test data. The near-limitless diversity of substances that can be engineered from one particular composition can result in some nanoparticles being designed to confer health benefits, while others may become toxic, be harmless, or retain the toxicity profile of their bulk counterparts.

Traditionally, classification of particles has been conducted on the basis of size due to the principle that as particle size decreases, the greater the potential impact on human health, because the particles can be more easily inhaled [2]. Additionally, numerous reports exist in the published literature showing that the toxicity of particles (on a mass basis) generally increases as their size decreases. The terms *nanoparticles* (NPs) and *ultrafine particles* (UFP) describe particles in the same size range (less than 100 nm), but *nanoparticles* usually refer to manufactured/engineered materials while *ultrafine particles* are defined as naturally occurring or those arising in ambient air [3].

It has been demonstrated in the literature that changes in a particle's physical characteristics (e.g. size, shape, aspect ratio, surface area, surface coatings, and chemical composition, impurities and crystalline structure) will influence the particle's environmental fate [4] and toxicological properties [5]. The relationship between a particle's physical characteristics and toxicity has been further emphasised in a mini review by Warheit [6].

To better evaluate the human health risk arising from exposure to engineered nanomaterials, a particle assessment framework has been developed (Figure 1). It is proposed as a logical paradigm for the assessment of particles under existing regulatory frameworks. In addition, it constitutes a concern-driven approach to focus future toxicity testing

requirements for particles. Using the approach outlined herein should lead to more focused toxicological testing and a more tailored risk assessment of new particulate substances, including nanoparticles.

Disclaimer: The views expressed in this paper are solely those of the author and do not necessarily reflect those of the U.S. Environmental Protection Agency. Mention of trade names or commercial products does not constitute endorsement or recommendation for use by the Agency.

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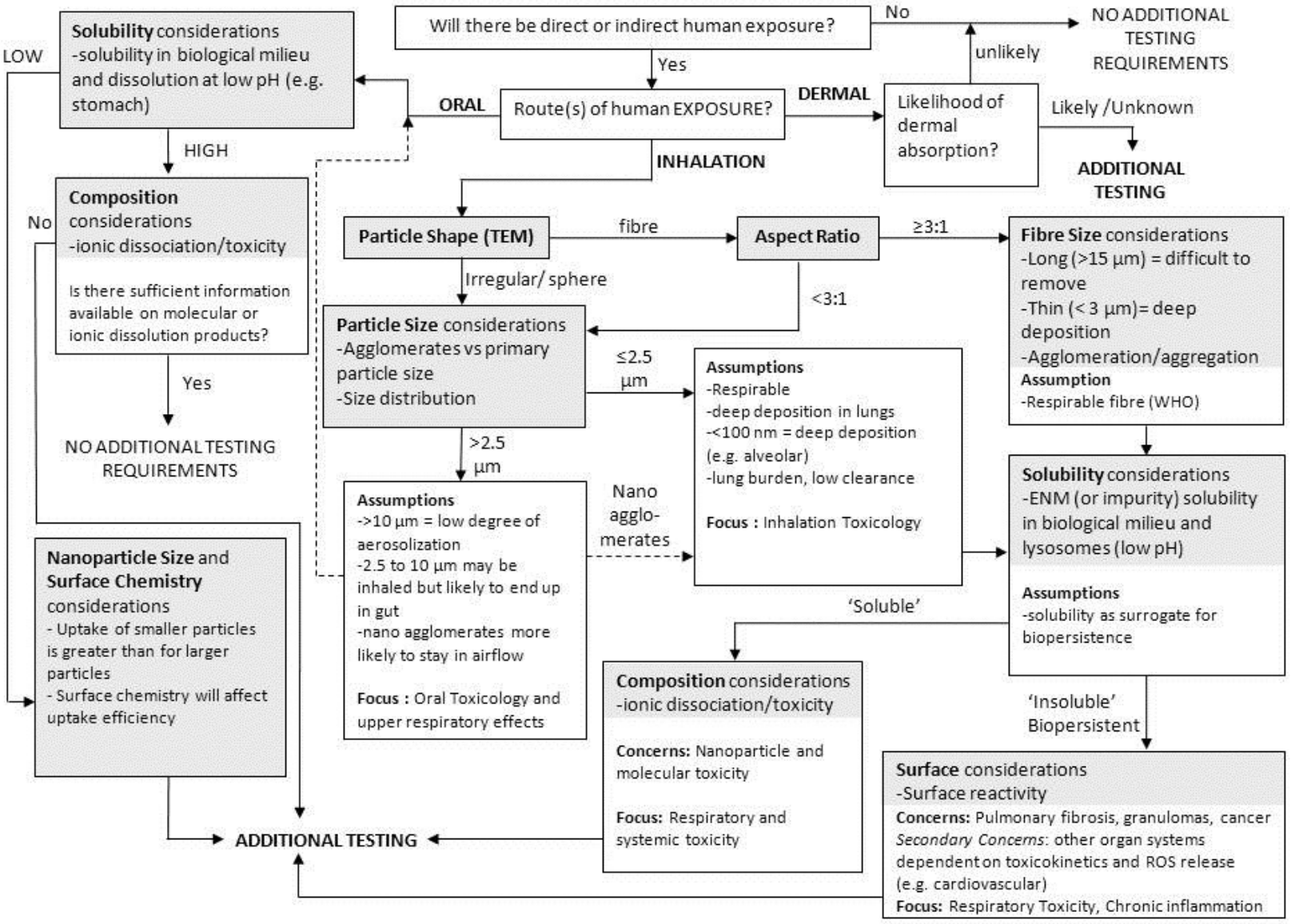

Figure 1: Schematic for focusing concerns and additional testing requirement for novel nanoparticles

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