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When enough is enough

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The European Commission should be regulating nanosilver, not asking for yet another report on its impact on health and the environment.

In December 2011 the European Commission asked its Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to provide a scientific opinion on nanosilver[1]. Specifically, this committee, which consists of independent scientists appointed by the Commission, is being asked to answer four questions under the general heading of 'Nanosilver: safety, health and environmental effects, and role in antimicrobial resistance'. However, most of these questions (and possibly all of them) have already been addressed by no less than 18 review articles in scientific journals, the oldest dating back to 2008[2–4], plus at least seven more reviews and reports commissioned and/or funded by governments and other organizations (Table 1). This raises an important question: when will governments and regulatory agencies stop asking for more reports and reviews, and start taking regulatory action?

> Many of these reviews and reports go through the same literature, cover the same ground and identify many of the same data gaps and research needs.

In 2008, Sam Luoma (University of California, Davis) opened what now seems to be Pandora's silver box with his excellent overview of nanosilver and the environment[3]. In 2009, six reviews were published on this topic[5–10], including reports commissioned by the Department of Environment, Food and Rural Affairs (DEFRA) in the UK[6], the Federal Ministry of Food, Agriculture and Consumer Protection (BfR) in Germany[7] and the National Institute for Public Health and the Environment (RIVM) in the Netherlands[8]. One of the two vice-chairs of SCENIHR, Wim De Jong (RIVM), also co-authored a review article in the journal *Nanotoxicology* that is now one of the most cited papers in the field[10].

A further eight review articles in scientific journals followed in 2010[11–18], plus substantial reports commissioned by the Environmental Protection Agency (EPA) in the US (which ran to 221 pages)[19] and the Joint Research Centre (JRC) of the European Commission (426 pages)[20]. Two of the review articles in journals were also funded by the European Commission[14,16]. And 2011 saw the publication of five more review articles on nanosilver in scientific journals[21–25], plus a 136-page report from the Danish Environmental Protection Agency (Danish EPA) about nanosilver and six other nanomaterials[26].

Many of these reviews and reports go through the same literature, cover the same ground and identify many of the same data gaps and research needs. Hence, we predict that the SCENIHR's upcoming review will consist of five main sections summarizing: the properties and uses of nanosilver; human and environmental toxicity; microbial resistance; risk assessment; and research needs[3,8,10,14,16,18–20,24–26]. We also predict that the SCENIHR's report will say something along the following lines: "Nanosilver is reportedly one of the most widely used nanomaterials in consumer products today but the scale of production and use is unknown. The antibacterial properties of nanosilver are exploited in a very diverse set of products and applications including dietary supplements, personal care products, powdered colours, textile, paper, kitchenware and food storage." And like many previous reviews and reports[3,10,14,18–21,25,26], the new report is likely to cite the Consumer Product Inventory maintained by the Project on Emerging Nanotechnologies[27].

After reviewing the literature on human toxicity, there is a good chance that the SCENIHR will say that the toxicity of silver metal is generally considered to be relatively low, while noting that a non-life-threatening bluish–grey discolouring of the skin has been found only after high and repeated ingestion or inhalation of colloidal silver[2,3,10,20,21,24,26]. And the conclusions will probably echo those of the highly cited review published in *Nanotoxicology* in 2009 and several other recent reviews[6,14,20,23] by saying something along the following lines: the number of well-controlled studies on the potential toxicities of nanosilver as well as the current knowledge of the kinetics of nanosilver is too limited to provide a proper foundation of human risk assessment. The SCENIHR is also likely to note that nanosilver has been found to be absorbed and distributed to target organs (such as the liver, lungs and olfactory bulb), and to have caused inflammation and liver damage in rodents after oral exposure. And increases in the production of reactive oxygen species *in vitro*[10,14,16,19,20,26] will probably be mentioned as well.

On the environmental toxicity front, the SCENIHR is likely to state something very general about it being well known that both bulk silver and nanosilver are potentially toxic to the environment with the concentration that causes an adverse effect in 50% of a population being in the lower parts-per-billion range for aquatic organisms[3,20,23,26]. Moreover, because inhibition of nitrifying bacteria by nanosilver has been observed in the very few original studies that have been published, the SCENIHR will have to consider this topic under the heading of 'Other environmental, health and safety (EHS) issues' because this phenomenon might affect the proper functioning of wastewater treatment plants[20,23,26]. It remains uncertain whether nanosilver is more toxic than ionic silver, the report is likely to say, because the effects seen in many cases can be ascribed to ionic silver: however, some studies have documented a more pronounced effect associated with nanosilver, but the data is inconclusive[2,9,19,22,24,25].

Because there have been very few original studies of the relationship between nanosilver and the development of antimicrobial resistance (less than five to the best of our knowledge), it is likely that the SCENIHR will rely heavily on the seven review articles that have addressed this topic[3,7,10,15,17,19,25]. Evidence that the increasing use of nanosilver may be leading to bacterial and fungal resistance towards silver include reports of resistance to silver-based burn dressings (originally published in the mid-1970s and reviewed

Table 1 | Many of the reviews on nanosilver that have been published since 2008 (first column) have already addressed the four questions on the environmental, health and safety (EHS) aspects of nanosilver that the SCENIHR was recently asked to review. Page numbers for the part(s) of each review that are relevant to these questions are listed in columns 2–5.

Reference	Human health and the environmental implications?	Increase in selection of silver-resistant microorganisms?	Reduction in the efficacy of nanosilver?	Other EHS issues?
Chen and Schluesener[2]	1–12	27		
Luoma[3]	25–35			
Panyala *et al.*[4]	119–124			
Sharma *et al.*[5]	93–94		89–93	
DEFRA (UK)[6]	71, 73, 80, 97–100, 139, 142, 145			97
BfR (Germany)[7]		3–6		
RIVM (Netherlands)[8]	29–41			
Rai *et al.*[9]	82		77–81	
Wijnhoven *et al.*[10]	111–114, 121–131	116	115–116	
Ahamed *et al.*[11]	1842–1846			
Cao and Liu[12]			673–674	
Chaloupka *et al.*[13]	585		581–585	
Christensen *et al.*[14]	286–294			
Duran *et al.*[15]	954–956	951–952	952–954	
Johnston *et al.*[16]	330–342			
Marambio-Jones and Hoek[17]	1539, 1543–154	1531–1538	1542–1543	
Quadros and Marr[18]	776–779			
EPA (US)[19]	98–133	19–20, 74		134–146
JRC (EC)[20]	121–137, 212–217, 305–325			
Fabrega *et al.*[21]	518–529		527–528	
Gangwal *et al.*[22]	1539–1546			
Musee *et al.*[23]			1169–1174	1179
Nowack *et al.*[24]	1180–1182			
Stensberg *et al.*[25]	880–882	881		
Danish EPA[26]	74–88			

in refs 3,7)[28,29] and the finding that 10% of the intestinal bacteria tested randomly in a Chicago hospital had genes that are resistant to silver ions (originally published in 2003 and reviewed in ref. 17)[30]. However, citing a leading article[31] that was published in the *Journal of Antimicrobial Chemotherapy* in 2007, the reviews collectively conclude that further studies on antimicrobial resistance are needed because there are currently no standardized methods for testing the antimicrobial activity of silver. (This is partly because the solubility of nanosilver is not fully understood, and the solubility influences the bioavailability which, in turn, influences the sensitivity of silver-resistant and silver-sensitive bacteria[17].) Finally, we predict that the SCENIHR will underline the importance of silver speciation as this has been a general theme in many previous reviews[3,11,14,16,18–20,24–26].

The SCENIHR review is due to come out in early 2013. Although the committee can call on additional expertise from outside experts within the specific subject, one permanent committee member often acts as a rapporteur and prepares a draft opinion that is voted on. Given the many high-profile reviews already available, we find it unlikely that the scientific committee will reach any significant new insights. One wonders, therefore, why the European Commission has asked for yet another review on this topic.

> By initiating one review after the other, regulators have created an unfortunate situation of 'paralysis by analysis'.

No regulatory action has so far been taken to limit human and environmental exposure of nanosilver. Although it may be common practice for regulators to ask for 'their own review' from a scientific advisory group, rather than acting on reviews published as scientific papers, it seems that many of these reviews have been commissioned by regulators with a purpose of delaying decisions on regulatory measures that should be implemented. It would not be the first time that regulators are 'buying time' before making difficult decisions that will be against the interests of certain stakeholders[32]. Although it is clear that the SCENIHR cannot decline requests from the European Commission for scientific opinions, it seems that the committee is being used by the Commission to stall the regulatory decision-making process until 2013. By initiating one review after the other, regulators have created an unfortunate situation of 'paralysis by analysis' because reviews tend to identify additional research needs rather than the options for optimal regulatory policies.

We acknowledge that answering the question of how to regulate the use of nanosilver is not easy given the different views of the different stakeholders in this debate and the complex regulatory landscape associated with the many applications of nanosilver. However, some of the reviews already published offer plenty of recommendations on actions that could be taken. Back in 2008, for example, Luoma[3]

sketched out a multi-faceted strategy that included: (1) the development of clear rules defining the ingredients of a product using the unique physical and chemical attributes of the ingredients to track production, use and environmental release/dispersal data; (2) the assessment of what information is needed to oversee safe use of nanosilver; (3) the evaluation of the relevance and shortcomings of current silver-relevant regulations. In 2009, DEFRA in the UK recommended the application of the precautionary principle[6], whereas the BfR in Germany urged producers not to use nanosilver in foods and everyday products[7]. However, little progress has been made in implementing any of these recommendations.

Arguably, we all want that the pros and cons of regulatory policy options be based on the best available science while taking broader socio-economical and ethical aspects into consideration before deciding on the appropriate regulatory measures concerning human and environmental exposure to nanosilver. Although it is common for independent scientific experts to be commissioned to gather, analyse and review the available scientific information, and to provide recommendations on how to address a given risk, we do not see the need for further reviews. It is time for the European Commission to decide on the regulatory measures that are appropriate for nanosilver. These measures should then be implemented wholeheartedly and their effectiveness monitored. ❐

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