ADVISORY COMMITTEE ON HAZARDOUS SUBSTANCES

REPORT ON NANOSILVER

Background

1. At its 32nd meeting in March 2009 Defra requested guidance on nanosilver from the Committee. Paper ACHS/09/02 invited the Committee to:

I. Review information and studies on the environmental exposure and effects of nanoparticulate silver;
II. Comment on known or predicted environmental exposure levels and whether these present a human health or environmental risk;
III. Comment on the nature of appropriate measures to minimise risks, if these are felt to be necessary at this point in time;
IV. Consider what action should be taken to further develop our understanding in this area.

2. The Committee appointed Dr Jamie Lead as its rapporteur for this work and held discussions at its March, June and September meetings – the outcome of which is this report.

3. This paper deals with points (I), (II), and (IV), but is primarily concerned with environmental exposure and hazard and only briefly deals with human health. Risk management issues (point (III)) are not discussed as there is not sufficient information to comment on appropriate measures to minimise risks, and these are the responsibility of the relevant policy and regulatory bodies.

Introduction

4. Silver is well known as a bacteriocide and this short report does not consider dissolved silver or organic compounds of silver but only nanoscale silver (nanosilver). Nanoscience and nanotechnology deal with the nanoscale, which is generally defined as being between 1-100 nm. At this scale, novel and unusual properties may be displayed due to increased specific surface area, surface reactivity and quantum-related effects. These properties are being exploited commercially and these novel, unknown and unusual properties potentially have implications for human health and environmental health. Thus, when we consider nanosilver, we must consider the potential impacts of silver and of any novel toxicological or environmental properties due to silver being in the nano-form. These novel effects by definition may not be currently known but an example is the possibility of the nanosilver acting as a 'Trojan Horse' *i.e.* the nano-form may be more bioavailable than the inorganic, dissolved form and once in or on a cell, the nanosilver may act as a concentrated and long term source of silver to the cell. The nanoform may also have unusual toxicity mechanisms not seen in the traditional pollutant.

Discussion

5. In addition to known hazards from silver, there is now evidence that there is likely to be wide exposure to low concentrations of nanosilver in the environment. The Woodrow Wilson database[1], which shows numbers of consumer products on the market claiming to contain nanomaterials in some form, shows that by far the greatest number of products use silver. Nanosilver is used in cosmetics, fabrics, toothpaste and toothbrushes, kitchen and other surfaces, plasters and medical equipment to name a few and nanosilver has been shown to be released from commercially available products (*Benn and Westerhoff*, 2008).

Building on this, three published studies have shown wide exposure of nanosilver in the environment (*Blaser et al*, 2008; *Luoma*, 2008; *Mueller and Nowack*, 2008). There are three points which require discussion in relation to these studies:

i. It is not currently possible to analytically distinguish nanosilver from other forms of silver in the environment. The studies above are purely from modelled data based on known or estimated usage, fraction of nanosilver within each product and likely behaviour of the nanosilver once in the environment. The models have thus not been parameterised, as no quantitative data exists.

ii. The modelling/exposure studies mentioned reach different conclusions.
The *Blaser et al* study suggests that values of PEC/PNEC > 1 (PEC – predicted environmental concentrations; PNEC – predicted no effect concentrations) cannot be ruled out in freshwaters ecosystems because of our lack of knowledge.
The *Mueller and Nowack* study suggests that the risk from nanosilver is likely to be low based on their calculated PEC/PNEC ratios. *Mueller and Nowack* state quite correctly that we are at a very early stage in our understanding and their conclusions could change as information becomes available. As well as the uncertainties from point (i). above, the PNEC value used was derived from a single study. The study showed lowest observed effects concentration (LOEC) of 40 mg L^{-1}, which is high compared with a number of more recent studies. *Mueller and Nowack* assumed a safety factor of 1000, giving a PNEC of 40 μg L^{-1}.
The *Luoma* study agreed here in as much as it was suggested that nanosilver concentrations are unlikely to rise above 1 μg L^{-1} in any environmental compartment. However, the *Luoma* study quoted values for dissolved silver, with LOEC values at 10 ng L^{-1}, several orders of magnitude lower than in the *Mueller and Nowack* study. However the 10 ng L^{-1} LOEC value was derived from studies on dissolved silver.

If one assumes that (a) all the nanosilver modelled in *Mueller and Nowack* paper will become dissolved in the environment; (b) PEC values are approximately 80 ng L^{-1}, possibly rising to ca 1 μg L^{-1} as described by *Mueller and Nowack* and *Luoma* papers; (c) 10 ng L^{-1} is the true LOEC for dissolved

[1] http://www.nanotechproject.org/inventories/consumer/

silver; it is possible to conclude that the PEC/PNEC value is substantially higher than 1, which is a cause of concern.

There are of course a number of uncertainties due to the current lack of knowledge. In this scenario, nanosilver itself is of limited hazard as it dissolves quickly but the dissolved silver produced may have risk associated with it and can be dealt with using standard risk assessment procedures. A second scenario is that the nanosilver does not dissolve rapidly and this brings with it a number of uncertainties associated the nanoform of silver. Research into dissolution of nanosilver under environmentally relevant timescales and conditions is thus a high priority.

iii. Point (ii) above is based on a use of mass based concentrations and the appropriate metrics for toxicology experiments are widely discussed. Other suggestions such as number or surface area based concentrations have been discussed and, in some cases, these metrics have been shown to relate directly to toxicity (*Klaine et al,* 2008).

6. *The nature of the environmental risk associated with the widespread use of nanosilver products is poorly characterised due to lack of knowledge*. Persistence and dissolution are critical parameters in order to understand whether there is a risk from the nanosilver itself or whether there is a risk from produced dissolved silver, where conventional risk assessments can be used. The likely wide use of consumer products using nanosilver as an antibacterial agent suggests wide environmental exposure. Available data suggests that the most sensitive species to nanosilver so far tested are likely to be invertebrates and unicellular organisms such as bacteria. Higher organisms such as fish, and also humans, may be less sensitive. However, in addition to direct toxicity, there are questions of silver resistance by bacteria in response to low concentrations which are widespread in the environment and which could compound problems observed with antibiotic resistance (*Silver et al*, 2006). Silver resistance, and possible increased antibiotic resistance due to nanosilver usage is an area of limited or no knowledge but has the potential to be deleterious to human health and should be investigated.

7. A further and very important question is whether there are direct problems associated with nanosilver. The available data allow no definite conclusion to be drawn and data cannot easily be rationalised. In part this is due to the poorly controlled and characterised physical and chemical properties of the nanosilver used in research to date. However, there are indications that toxicity is apparent in the nanosilver form and that there is a specific 'nano-effect' (*Lok et al*, 2006; *Griffitt et al*, 2008; *Lee et al*, 2008; *Ashrani et al*, 2008; *Navarro et al*, 2008). Further research is urgently required.

8. Additionally, there are a number of unvalidated assumptions in all exposure models discussed, the most important being a lack of baseline data on actual environmental concentrations of nanosilver. In addition, to take the *Mueller and Nowack* study as an example, only Swiss conditions were considered with no reference to movement of material across the borders and no reference to practices in other countries

(Switzerland does not use sewage sludge to amend agricultural soils, for instance). In most of these studies, all relevant environmental compartments need to be included; assumptions related to behaviour of nanoparticles in the wastewater systems and incinerators were made in the absence of data on nanosilver behaviour in such systems. The models are easily adjusted, and development has already continued apace, but parameterisation with experimental data is lacking.

Conclusions

9. A good deal of information is now available on hazard and some on exposure. However, due to difficulties in material properties and characterisation, primarily, it is not possible to fully rationalise often disparate (eco)toxicology results.

10. Exposure levels in the environment are not known and modelled concentrations are approximately 100 ng L^{-1} currently, with values potentially rising to 1 μg L^{-1}, possibly more, dependent on uses, increase in usage and the behaviour of nanosilver within the environment. These aspects are incompletely understood. Lack of analytical techniques means that it is impossible to fully validate these models. Data reported gives widely different values of biological effects. However, estimated PEC/ PNEC ratios do give cause for concern for environmental health. PEC/PNEC ratios, may, of course, be insufficient when investigating risk of nanoparticles. Exposure to humans is likely to be high in certain groups, due to their use in a wide range of products.

Recommendations for further action

11. Further knowledge on both hazard and exposure is urgently required, given the large uncertainties identified in this document. Direct funding and leveraging of other funding sources are suggested as mechanisms to fund immediate priorities:

- (i) Development of methods to quantify nanosilver in the environment;
- (ii) Understanding fate and behaviour processes (transport and persistence), especially to identify environmental 'hotspots' with high mass or particle number concentration;
- (iii) Understanding biological effects (bioaccumulation, toxicity) under realistic conditions.

12. Specifically, it is suggested that the relevant government bodies immediately fund a thorough review of this area including the peer-reviewed literature, grey literature and research projects in progress and recently completed. This review should lead up to a workshop which brings together relevant stakeholders. The workshop should focus in knowledge exchange between stakeholders, development of a coherent and integrated research strategy and medium term horizon scanning (developments in the next 5-10 years).

13. A further immediate research objective should be a *critical* review identification and inventory of uses and products containing nanosilver, amounts within products and

their likely release rates. This must specifically include laboratory based measurements of specific consumer products.

14. A final research objective for immediate funding is to identify partitioning of nanosilver between different environmental compartments, again using small scale laboratory experiments to parameterise the exposure models mentioned above (e.g. *Mueller and Nowack*, 2008; *Blaser et al*, 2008, *Luoma*, 2008). This would include partitioning in sewage treatment works, between water and sediment and other relevant environmental compartments.

15. In addition, in the medium to long term, relevant governments departments should work with other funders *e.g.* the research councils, EU etc, to address a number of specific areas:

a. In what products is nanosilver used, at what concentrations and what are the release rates to the environment?
b. What are the main routes of exposure?
c. What are actual measured concentrations of nanosilver in the environment and how can they best be monitored?
d. How does nanosilver change once in the environment?
e. What is the fate and behaviour of nanosilver in the environment? How does nanosilver partition into different compartments and how does it distribute between the dissolved, dispersed and aggregated forms?
f. Is nanosilver persistent, bioavailable and toxic under realistic conditions?
g. Does trophic transfer occur?
h. Are there novel mechanisms of toxicity caused by silver being in the nanoform?
i. How do toxicity and toxic mechanisms vary with differences in nanosilver and differences between species?
j. What are the most relevant conditions for toxicity tests for nanosilver?
k. Are there any implications for bacterial resistance to either silver itself or to antibiotics from widespread use of nanosilver?
l. How do these behaviours and properties relate to nanoparticle properties (size, charge, stabilisation, aggregation, purity, specific surface area etc)?

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