

Nanotechnology study

Regulators meeting 11 February 2004—summary of discussions

Environment and Food session

Prof. Roland Clift noted that the working group were keen to discuss exposure pathways of nanoparticles, and how this may affect current and future regulations. The working group was also interested to learn the extent to which current chemical regulations might be applied to nanoparticles.

The session began with a short talk by Dr. Martin Williams from DEFRA with expertise in environmental air quality. He noted that regulators had previously focussed on airborne particles of size larger than 10 microns (PM10), but now the focus is moving towards finer and finer particles down to 2.5 microns (PM2.5). Measurements of these size fractions has been carried out on a mass basis; however measurement of total mass alone would not give any information on the numbers or size distribution of nanoparticles. Measures are already in place to reduce mass emissions of PM10 and PM2.5, many of which will also reduce nanoparticles. This has however introduced what he termed the 'regulators dilemma': smaller particles tend to condense on larger particles, and as the amount of the larger particles are controlled, there is the possibility that the number of airborne particles might not reduce. Up until a few years ago there had been virtually no measurements of nanoparticle numbers or size distributions in the ambient environment. Defra currently has a programme of such measurements at four sites in the UK, providing continuous data, however there are currently significant technical challenges to achieving this. He noted that current regulations related to air quality focus on mass, informed by the evidence from the health effects community, which as yet has concluded that there is insufficient evidence to relate adverse effects to nanoparticles and thus to formulate air quality standards. In the area of vehicle emission regulation however, there is an initiative under way to develop a regulatory measurement method for nanoparticles based on number rather than mass which could be used to underpin any new standards for nanoparticles which might eventually emerge. The UK was taking a lead on this. He recognised that due to the issues listed above, if air quality standards were to be based on nanoparticles, the regulatory measurement method would need to be defined carefully.

The next short presentation was given by Dr. Colin Church from DEFRA whose interest is industrial chemicals. He explained that the current regulations are based on a classical risk assessment of bulk properties, with no consideration given to size, and that chemicals are divided into two categories : existing substances and new substances. Existing substances are defined by the European Union as those declared on the market in September 1981, new substances are those declared after that date. The majority (over 100,000) of chemicals on the market today are classed as existing substances, which have a much lower requirement for testing and assessment than new substances. The EU is in the process of setting up a new framework to combine existing and new substances (Registration, Evaluation, Authorisation of Chemicals (REACH)), which will set a basic level of assessment required for chemicals produced above 1 tonne per year. This will not however demand that particle size is taken into account.

Professor Mike Depledge from the Environment Agency then gave a brief talk. He stated that the environment agency is aware of nanotechnology and is particularly interested in the potential benefits it may offer. He noted that due to the changing properties of existing chemicals when particle size is reduced to the nanoscale, it may be necessary to re-evaluate toxicology. There is currently however no established mechanism for testing for the potential toxicological effects that nanoparticles may have on humans and the

environment. It was noted that testing and assessment levels are currently triggered by mass, and as nanoparticles may be produced in small quantities (low total mass), the corresponding requirement for testing would also be low, and perhaps too low. It was thought that the current levels of evidence and knowledge surrounding nanoparticle toxicity were insufficient to base regulations on, and that more work was required. Implementation of the precautionary principle however may harm industries utilising nanoparticles by imposing unwarranted costs. Any possible ecological impact that a release of nanoparticles may have on the environment and animal life was thought to be completely unknown. The issue of public perception was then raised, and it was noted that this can impact on regulation, as had happened with GM.

Attendees were then asked how the regulatory system for air quality might move from mass (assuming this isn't the relevant metric for nanoparticles) to particle number as is being considered for vehicle emissions regulation. It was felt that measurement by particle number would be feasible, however there would be problems in determining what the chemical composition of the sample is. Also, there must be a clear understanding about why size is the relevant metric for a particular chemical, and what the implications of this will be. It was thought that this knowledge is currently lacking. There was a feeling that regulation by particle number rather than mass would be more precautionary and one attendee advised that it should be phased in gradually in order to avoid hampering industry. Another attendee felt strongly that a move away from mass to particle number could result in the exclusion of some chemicals or skew the whole regulatory picture. He felt that very good evidence should first be supplied before moving to a particle number based system, as for some substances mass is the relevant metric while for others particle number may be. One attendee then noted that other properties such as solubility and surface area may also be important to consider. The opinion was then expressed that all good regulation is based on evidence that a wide range of people can accept, but it was thought that evidence on the eco-toxicity of nanoparticles is currently non-existent. In addition, agreed methodology for the testing of nanoparticle toxicity in the environment is not in place and it was felt this was an area that the scientific community should address.

Besides the potential intrinsic toxicity of nanoparticles, it was suggested that due to their high relative surface area, nanoparticles may act as vehicles for toxin absorption into the body, however no direct evidence was thought to exist to support this.

Prof. Clift then noted that attention appeared to be focussed on the possible adverse health effects of nanoparticles on humans through inhalation or skin absorption, but not through ingestion. It was pointed out that the digestive tract is actually designed to absorb small particles, however it was thought that little or no work had been done relating to nanoparticles. A representative from the food standards agency stated that they had an interest in nanotechnology, however there was not a great deal of knowledge on the subject yet. Food additives that may fall under the heading of nanotechnology were thought to be gold, silver and titanium dioxide which can be used as colourants. The view was then expressed that a great deal of work has been done in the pharmaceutical sciences regarding the fate of ingested nanoparticles in the body, and that it is possible to predict where particles can end up based on their size.

A member of the working group then asked attendees what the current triggers are that prompt regulators to investigate something. One attendee stated that evidence of an adverse health or environmental effect was required, and regarding the issue of nanoparticles, noted that the environment is and has been exposed to nanoparticles (both natural and synthetic) for some time however there has been no great cause for concern. Representatives from DEFRA and the Environment Agency both utilise horizon scanning and have identified nanotechnology as a possible area of interest, however would only look to avoid the potential problems when the weight of evidence becomes sufficient. A member of the working group then asked if

regulators took steps against substances before their effects were ascertained, and attendees responded that this was not done however interim guidelines were issued in order to minimise the chance of potential problems occurring.

The issue of testing was then discussed and one attendee felt that the UK lacked coordination in this area. Another attendee then noted that regulators are moving towards this task. There was also concern expressed that planned closures of environmental epidemiology testing centres will reduce expertise in this area in the UK. Representatives from the Environmental Agency were also concerned that test centres for eco-toxicology were not funded or supported adequately. It was felt that there was a lack of research into ecotoxicology but the recently founded environmental research funders forum would shortly be considering nanotechnology as a possible priority for funding.

It was noted that at the moment the onus is on the producer to provide toxicological evidence at specific mass trigger levels of production. It was noted however that within the current framework (and the new REACH regulations) triggers for toxicity testing are by mass, with no consideration given to particle size or number except for fibres such as asbestos. Thus any currently regulated chemical can be produced at a smaller particle size without the obligation to inform regulators. The potential threat to ecosystems was then raised again with respect to the need for a coordinated approach to setting testing methodologies. One attendee then informed the group of an action plan from the European Commission aimed at merging environment and health at a national and global level which may help to address some of these issues.

The issue of uncertainty was then discussed, and it was suggested that the uncertainties surrounding the properties and impacts of nanoparticles was perhaps higher than for other chemicals. This issue was then related to public perception, and it was suggested that the regulatory process can be influenced by the public's perception which can be formed to some extent by the way that the media present the information. There is a clear need therefore for an open and transparent treatment of evidence during the regulatory process, and one attendee cited the Food Standards Agency as a model organisation in this respect. Another attendee felt that there is a need for a higher standard of measurement and that the data that does exist should be much more widely available, which would assist in the agreement of international standards.

A member of the working group then asked for clarification as to whether measurement and control of nanoparticles per se was necessary, or whether only certain nanoparticles required attention. An attendee felt that current evidence on inhalation toxicity suggested that size does matter, but that type mattered less so, and this led to the suggestion that particle size should be the main metric when assessing potential adverse health effects of nanoparticles.

One attendee noted that where uncertainties exist in the evidence, one driver for regulations can come from a demand from the public, and questioned whether an example existed of where such regulations were subsequently relaxed in the light of new evidence. Attendees generally felt that examples of this kind were very rare, however noted one example on air quality standards from America in the 1970's.

The attendees were then asked if they felt the current regulatory approach to environmental regulations is fair and balanced. One attendee stated that regulators make a judgment of the balance between risks and benefits before determining the need to regulate, but that action cannot be taken in the absence of evidence. With regard to nanoparticles, the attendee felt that the form of current regulations would suffice, however scientific and technical information required to implement those regulations are lacking.

The view was then presented by a member of the working group that large numbers of nanoparticles will not be manufactured by industry for use in their intrinsic form, but that 99.9% of them would be incorporated into components and devices. Therefore there is a need for a cradle to grave approach when considering regulations. This raised the issue of possible gaps in the regulatory framework when dealing with the complete lifecycle of products, and it was felt that while some regulation was in place for dealing with the disposal of computers and monitors etc (EU WEE), a great many products were not regulated during disposal or in-life use. It was pointed out that this was not specific to nanotechnology.

The working group were then keen to explore how cost-benefit analysis was carried out by regulators. An example was given of a nanoparticle fuel additive which reduces fuel consumption, and hence CO₂ emissions, but where the potential environmental effects of the additive are unknown. One attendee noted that regulators also consider non-financial costs and benefits, and felt that Government and society determined where to set the balance. It was noted that toxicological testing is carried out by the producer, however where necessary, this is also examined by an external independent body, and this was felt to be satisfactory. When asked whether testing of nanoparticles may prove to be prohibitively expensive for industry to undertake, and hence may stifle progress, one attendee suggested that not all particles would require testing as their properties could be surmised by 'read-across' (analogy with similar particles), or by modelling.

One attendee then raised the question of the use of animals in chemicals testing, and suggested that the move to the new chemical regulatory framework (REACH) will increase the use of animals from 2.7m to 6m per year, due to additional testing requirements. He felt that while testing may be necessary in some cases, there are insufficient funds being directed towards the use of alternatives to animals.

An attendee then pointed out that if regulation is put in place to cover nanoparticles in the environment or workplace, compliance may become an issue as no agreed methods exist to monitor or measure particle levels.

Medical devices, Medicinal products, Health and Safety and Cosmetics session

Prof. Seaton began by reflecting on the issues that had arisen in the previous session. In particular, that there is a change in properties between chemicals in their large and small particulate forms, but also that nanoparticles have existed in the environment since before humans. Humans have thus evolved in an environment rich in nanoparticles, and therefore it might be expected that they have developed physiology that can deal with them. Whether new or synthetic nanoparticles may cause a problem however is currently in question. One problem which then arises is how to measure these 'new' nanoparticles against a background of 'old' nanoparticles, and whether this may present issues for regulators. As discussed in the first session, determination of the relevant metric, be it particle number, mass, surface area or reactivity, or a combination of these, is also an important issue. It was noted that regulators currently use mass as the relevant metric for chemicals, with the exception of fibres which are measured by number. The use of nanoparticles in cosmetics was mentioned, and attendees were asked to consider whether some cosmetics may be better regulated as medicines, as is done for example for sunscreens in the USA.

Rob Higgins from the MHRA (Medicines and Healthcare products Regulatory Agency) then gave a short presentation outlining the current approach to regulation of medical devices. He briefly described the three EU directives for medical devices:-

1. Active and implantable – this would cover pacemakers and cochlear implants for example.
2. Medical devices – this would apply to a very wide range of items such as walking sticks, dental materials, orthopaedic implants, electromedical equipment or x-ray machines.
3. In vitro diagnostics – this would cover instruments and test kits used to make a diagnosis from samples taken from the body.

For all these categories a risk/benefit analysis is done; the majority of medical devices require clinical data, toxicity data is necessary for products coming into contact with the body such as implants. Levels of risk for a particular product are determined by their importance to body function and potential for causing harm, e.g. artificial heart valves would qualify as a high risk product while walking sticks would be low. Testing of products is undertaken by the manufacturer with, in some cases, involvement of an independent notified body. Higher risk products require stricter testing with more involvement from these independent bodies, while low risk products such as walking sticks are generally self-declared by the manufacturer. The regulation surrounding medical devices is very general and flexible, and so the MHRA felt that nanotechnology related products would be covered. It was noted that the MHRA do carry out horizon scanning and were aware of potential medical applications of nanotechnology, however were unaware of any nanotechnology enabled products currently on the market.

The issue of risk assessment was then explored, and a hypothetical example of a walking stick which has been strengthened and lightened through the incorporation of carbon nanotubes was suggested to attendees. A representative from the MHRA felt that as the nanotubes would not be absorbed into the body, or be bio-active, that this new hypothetical walking stick would still be classed as low risk. Clarification was then requested, and it was confirmed by MHRA that if the walking stick however was impregnated with a drug (in nanoparticulate, or larger form) with ancillary action, it would be classed as high risk. It was then pointed out that full toxicity data on carbon nanotubes (which might be released through wear and tear) does not yet exist.

David Hook from the MHRA then spoke about the regulations for medicines. He noted that before medicinal products can be placed on the market, they must be authorised. This authorisation is based on quality, safety and efficacy, and is issued by the government following consideration of evidence. Risk/benefit is evaluated for patients, however it was noted that this is not the same as a risk/benefit analysis to the environment, though environmental impact is assessed *per se*.

The earlier discussion concerning the importance of measuring nanoparticle numbers was particularly interesting given that the usual metric for medicines dosage is mass. This might present challenges if it was necessary to redefine dosage in terms of particle numbers.

The issue of the definition of a medicine was then discussed and a representative from the MHRA noted that in the recent review of EU medicines legislation, the definition of a medicinal product has been clarified. This clarification reinforces the way products defined as medicines act on the human body and is intended to make clear the boundary between medicinal products and other products such as medical devices, cosmetics and food supplements. Where doubt existed about a product, a higher level of regulatory control is assigned. Products which are borderline in their definition between medicines and cosmetics, such as sunscreens were discussed however it was felt that their categorisation would not change as a result of nanotechnology. The fact that different countries regulate sunscreens as cosmetics and medicines was noted. When asked whether the MHRA actively consider products in this grey area, a representative mentioned that a 'borderline

substances' group exists within the agency to do just that. A member of the working group asked whether sunscreen could be described as a preventative medicine, and if so should it be re-classified as a medicine rather than a cosmetic. A representative from the MHRA responded by describing the potential impracticality of this move with an example:- the fluoridation of tap water to help prevent tooth decay would require water to be classed as a medicine, and taps as medical devices. If however a sunscreen product was promoted with claims to prevent disease then it could be considered a medicine if it met the definition. But otherwise, a cosmetic made unsafe using nanotechnology did not become a medicine – it remained an unsafe cosmetic. Regulation of cosmetics is not within the remit of the MHRA.

A member of the working group then was keen to clarify what was meant by risk, and whether a unit of risk existed that could be understood by scientists and the public alike. One attendee responded that a unit of risk did not exist per se, but that it could be described by a statistical chance that an event will occur. It was also felt important to put risk into context to avoid misrepresentation.

Representatives from the MHRA were then asked by the working group whether they were taking into account the changes in the properties of particles due to reduction in their size. They replied that they were very well aware of the significance of particle size for safety and efficacy and gave an example of a steroid inhaler which now requires half the previous dose of medicine due to reductions in the size of particles delivered. One attendee then raised the point that no regulations exist for medical devices at their end-of-life stage, and another furthered the discussion by noting that dispersion or disposal of cosmetics into the environment (e.g. sunscreens into the sea) was also not covered by regulations.

A member of the working group then asked whether new technologies such as nanotechnology were causing uncertainties to be different from those in the past. An attendee from the MHRA felt that the nature of the uncertainties has not changed, but that the degree has increased. It was also noted that difficulties were beginning to arise surrounding measurement.

Alex Tsavalos of the Health and Safety Executive (HSE) then gave a brief summary of their work into nanotechnology. He noted the broad remit of the HSE which focussed on safety in the workplace, but also covered some areas of consumer protection. The HSE have been looking at nanotechnology since early 2003, and while they have not seen large scale commercial manufacturing yet, they anticipate that if should this happen, it could ramp up very quickly. They believe that the possibility of nano-robots running amok, as in the grey goo scenario, is something that is so far off, if at all possible, that it does not need to be considered at present. Due to the generalisation that properties change with particle size, as indicated in past reviews of titanium dioxide and carbon black. The HSE has broken down issues surrounding nanoparticles into 3 categories: toxicology (including dermal penetration), explosion and occupational exposure. Currently the toxicology of nanoparticles is still undetermined but for possible dermal penetration of nanoparticles the HSE has seen some evidence that this is not an issue, however noted that the evidence is very scant. Issues of explosion were felt to be easy to understand and deal with. Regarding the workplace exposure to nanoparticles; the HSE has seen limited studies which have shown that with appropriate ventilation, higher concentrations of nanoparticles were actually observed outside the workplace than in. It was felt that as nanotechnology is not one technology, but a wide collection of many, that there is no need for specific 'nano' regulations, however the HSE felt that there may be a need in the future. HSE will keep the issue under review and would seek additional regulation if needed.

The criteria were outlined for the definition of a new substance as is set out in the Notification of New Substances (NONS) regulations, in particular that new substances are based on changes in chemical

formulation, not structure. For example, should a chemical that has been previously been produced in solid form, be made in particulate form, this would not qualify as a new substance. It was noted that NONS will be superseded by REACH, however as outlined earlier, this new system will not take changes in chemical properties as a result of reduction in particulate size into account. Issues surrounding the difficulty of measurement of particle size were then introduced and it was noted that the National Physical Laboratory (NPL) had greatly scaled down this part of their activity. It was felt that this technical ability must be built up again in order for a consistent internationally agreed standard for the measurement of nanoparticles to be reached. If nanoparticles cannot be measured in an agreed way, regulation cannot be enforced. The HSE noted that they are working on interim safety advice for laboratory workers who work with nanomaterials, and expect to distribute this in late spring. The advice will outline areas of concern, noting where there may be doubt in the scientific evidence, and give guidance on steps to decrease levels of risk.

The discussion then turned to where the responsibility and characterisation of hazard and risk lie. One attendee noted that it is the producer of the risk or hazard that has the legal responsibility, however with little publicly available information on the hazards of certain nanomaterials, risk assessment is difficult to carry out. There was an agreement that more basic toxicological research needs to be carried out and shared openly. A number of regulators made the general point that, in contrast to the USA, regulatory bodies in the UK do not have large budgets set aside for scientific research and development to conduct hazard assessments. Due to this restriction, agencies can only flag up issues. One attendee suggested that better partnership between Government, industry and academia should be encouraged to move the process forward. The attendee felt that the current process is very inefficient, with many research groups scattered widely, and that a coordinated approach to toxicity testing would be much more productive. It was thought however that issues of commercial confidentiality may hinder this framework. One attendee felt it important to have independent assessment however believed that this body of evidence should be properly catalogued and made more widely available. In the interim, basic preventative measures should be adopted to contain nanomaterials in the laboratory to prevent exposure to workers. Another pointed to the semiconductor industry as a model example of the containment and protection of its workers from harmful chemicals, however it was suggested that this was intended more to protect the integrity of the product than the health of the worker. Nevertheless, it was a good example of the successful containment of potentially harmful material in an industrial environment.

One attendee then suggested that grant applications should also have to include work on potential hazards to ensure that this work is done as early as possible. Another attendee felt that indications of potential hazard should be given as a bare minimum.

It was suggested that as the metric for regulating asbestos fibres is number, a similar methodology may be adopted for carbon nanotubes. It was noted however that facilities and the number of personnel with knowledge in the area of fibre counting have reduced dramatically in recent years, which may make implementation of such a system problematic. In addition it was felt that there is a general lack of knowledge regarding the type of new particle which may enter high-volume production in the future, and that this may present problems when developing measurement techniques for regulations.

One attendee who runs a laboratory which works on carbon nanotubes stated that he was aware of potential issues surrounding their safety, and has drafted guidelines for their use and handling within his lab. This involves the use of protective clothing and gloves, and the use of air filtration and ventilation systems. He noted however his fear that more dangerous pollutants may be being brought into the lab from a nearby car-park, through the air-intakes of the ventilation system. He noted that industrial production of carbon

nanotubes was currently low, however was starting to ramp-up, and expressed his concern that they are currently treated as carbon black although they may prove to have different levels of toxicity. A member of the HSE responded that he had not seen a translation of nanotube production from the lab into large scale industrial production, and that nanotubes that are used in the UK tend to be imported from overseas in a matrix for use as anti-static plastics, and so felt that the risks currently would be fairly low. Should the UK begin industrial production however, the HSE would examine processes very carefully. He also felt that new regulations would not be necessary for carbon nanotubes, but that guidance on their handling and toxicity may need to be produced. This should be done with the assistance of industry and other experts, bearing in mind the balance of risks and costs.

Rex Symons of the Better Regulation Taskforce then gave a brief summary of their five principles towards better regulation: proportionality, accountability, consistency, transparency and targeting. He felt it important that these principles were adhered to and that the possible benefits and opportunities that nanotechnology may offer were not missed.

The Chair then asked what regulators would like to see in the final report of the study, and what may create hindrances to the regulation of nanotechnology. One attendee said that he would like to see gaps in scientific knowledge identified that may prevent regulation from being formed. Another then re-iterated the view that the budget regulators have to conduct basic research is trivial compared to that seen in the USA, however it was suggested that this has lead regulators to engage with academia. A member of the working group then asked whether funds could be sought through the European Framework 6 program, however the low success rates for such proposals were noted.

Attendee list

Name	Affiliation
Ann Dowling	Nanotechnology working group
Roland Clift	Nanotechnology working group
Nicole Grobert	Nanotechnology working group
Deirdre Hutton	Nanotechnology working group
Ray Oliver	Nanotechnology working group
Onora O'Neill	Nanotechnology working group
Nick Pidgeon	Nanotechnology working group
John Ryan	Nanotechnology working group
Anthony Seaton	Nanotechnology working group
Saul Tendler	Nanotechnology working group
Mark Welland	Nanotechnology working group
Roger Whatmore	Nanotechnology working group
Andrew Dunn	Nanotechnology study secretariat
Sara Al-Bader	Nanotechnology study secretariat
Richard Ploszek	Nanotechnology study secretariat
Rachel Quinn	Nanotechnology study secretariat
Colin Church	Department for environment, food and rural affairs
Benjamin Dent	Department for environment, food and rural affairs
Michael Depledge	Environment Agency
Michael Festing	Animal Procedures Committee
Brian Fullam	Medicines and healthcare products regulatory agency
Glynis Griffiths	Food Standards Agency
Emma Hayes	Environment Agency
Rob Higgins	Medicines and healthcare products regulatory agency
David Hook	Medicines and healthcare products regulatory agency
Philippe Martin	EC-DG Health and consumer protection
Andrea Molyneaux	Medicines and healthcare products regulatory agency
Mike Murray	Association of the British Pharmaceutical Industry
Rex Symons	Better Regulation Taskforce
David Southerland	Department of trade and industry
Alex Tsavalos	Health and safety executive
Rita Wadey	Office of science and technology
Martin Williams	Department for environment, food and rural affairs
Alan Windle	University of Cambridge