



COMMITTEES ON TOXICITY, MUTAGENICITY AND CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT, COM, COC)

JOINT STATEMENT ON NANOMATERIAL TOXICOLOGY

Background

1. In June 2003 the UK Government commissioned the Royal Society, the UK national academy of science, and the Royal Academy of Engineering, the UK national academy of engineering, to carry out an independent study of likely developments in nanotechnology and of whether nanotechnology raises or is likely to raise new ethical, health and safety or social issues which are not covered by current regulation.¹ Their report "Nanoscience and nanotechnologies: opportunities and uncertainties" - was published on 29 July 2004.² The UK Government's response to the joint Royal Society and Royal Academy of Engineering report was published on 25 February 2005.³ The Committees on the Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COT, COC and COM) were identified in an annex to the Government report along with six other independent expert scientific committees as relevant scientific committees to provide advice on the development of nanotechnology. The Government stated in its reply to the Royal Society that it would ask for advice from COT/COC/COM on issues as they arise and seek to ensure that nanotechnologies will be explicitly mentioned in their terms of reference.

2. The COT, COC and COM carry out regular horizon scanning exercises as part of their annual remit (see appended internet links at the end of this statement). The COT identified nanomaterials as an emerging issue at its February 2004 meeting. Following the Royal Society's review of nanotechnology in 2004 (which was discussed at the COT's September 2004 meeting), all three committees identified the risk assessment of nanomaterials as an area of interest and asked for appropriate information to be provided for consideration.

Introduction to current review.

3. Overview papers on the available toxicological data were prepared for the committees to assist in preparing an initial joint statement.⁴⁻⁶ The information presented to the committees was based on a hazard assessment document published by the Health and Safety Executive (HSE)⁷, a literature

review prepared by the secretariat which identified a number of additional published scientific papers (which are cited in the overview papers) and information published in abstracts from the US Society of Toxicology (SOT) meeting held March 6–10, 2005, in New Orleans, Louisiana, USA.⁸ The HSE captured published information up to July 2004 and the additional review prepared for the committees captured information up to March 2005.

4. The Royal Society defined nanomaterials as having one dimension less than 100 nanometres (nm) or 0.1 micrometre (µm).² However, the Committees (COT, COC, COM) agreed that this should not be viewed as a rigid definition and that a pragmatic case-by-case approach should be adopted with regard to nanomaterials. There are two basic approaches to generating novel nanomaterials. ‘Top down’ technologies use machining and etching methods to create particulates which are usually found in micrometre sizes, but can also be produced in nanometre dimensions. Examples include engineered surfaces and surface coatings (e.g. fuel cells and catalysts) and microcrystalline materials (potential uses are in textiles, cosmetics, and paints). ‘Bottom-up’ nanotechnologies involve the production of nanomaterials from individual molecules. The nanomaterials thus generated are novel, e.g. carbon nanotubes and nanofoam, nanodots and fullerenes. Some examples of ‘bottom up’ nanomaterials are shown below. The committees noted that nanoparticles were also produced during combustion, food cooking and from vehicle exhausts.

	Carbon nanotubes	Fullerenes	Nanodots	Carbon nanofoam
Structure	Rolled up sheets of graphite, with one end capped	Molecules of carbon formed into hollow cage like structures	Crystalline structures of compounds eg cadmium, selenium, tellurium, sulphur	Clusters of carbon atoms in a web like structure
Properties	Extreme strength and electrical conductivity. Insoluble in water. Biologically non-degradable			Lightweight, spongy solid, can act as semiconductor. Magnetic property

5. Nanomaterials have a high surface to volume ratio. This means that a high proportion of the atoms will be at the particle surface, and consequently surface reactivity will be high. These particles may adopt structures that are different to the bulk form, with different physical and chemical properties. The kinetic behaviour of nanoparticles follows basic laws of gaseous diffusion, with extensive interactions between particles. It is likely these collisions lead to agglomeration, and reactions between nanoparticles and other airborne molecules (water or pollutants).⁷

COT/COC/COM Review of toxicological information on nanomaterials

Proposed approach to initial toxicological studies with nanomaterials

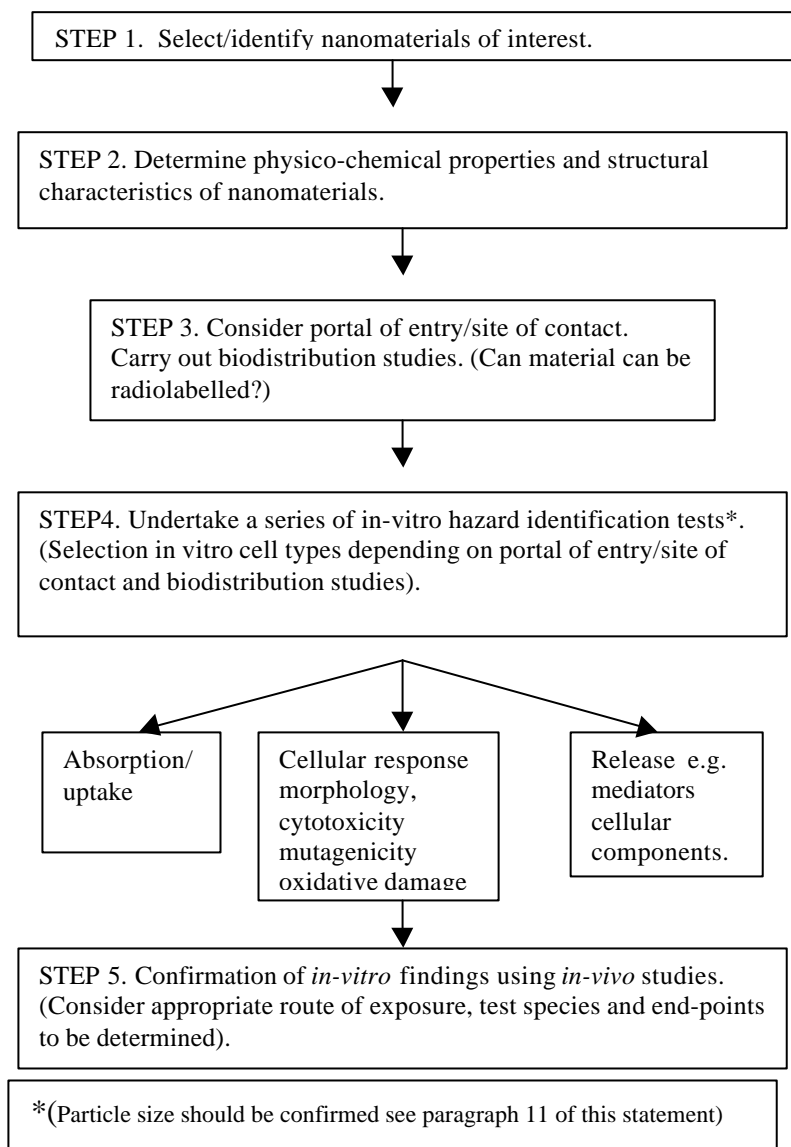
6. The Committees agreed that the objective of the review was to provide a baseline statement on the available information on nanomaterials toxicology. At the present time, there are considerable limitations in the number of materials tested, and in the toxicology data available. However, it is expected there will be considerable growth in the number of nanomaterials produced industrially and their potential commercial applications. There is also virtually no information on potential human exposure resulting from environmental exposure. To some extent this reflects the limited commercial applications to date (excluding medicinal/cosmetic uses which are considered under regulatory assessment schemes). In addition the review provided to COT/COC/COM did not cover the exposure to nanoparticulate material present in air pollution (e.g. resulting from industrial processes, diesel emissions etc). The Committees noted the importance of particle size, surface area and surface chemistry as determinants of nanomaterial toxicity. The main methods of hazard identification used included comparison of hazard data for micrometre sized and nanometre sized equivalent materials.

7. Possible biological effects were discussed, including a contribution of nanoparticles in the genesis of oxidative stress processes. It was suggested that the mechanisms leading to these processes probably depend on particle size and chemical composition. Some of the SOT abstracts reported studies suggesting that surface area might not be the most appropriate metric for describing the dose of nanoparticles, which contrasted with the information available in the HSE review document.^{7,8} The Committees noted the “Seaton” hypothesis regarding potential cardiovascular effects of inhaled particles.⁹ The Committee considered that there was scope for further research into the potential systemic effects associated with inhalation of nanomaterials. This would include information on uptake and systemic distribution and potential for systemic effects (such as procoagulation).

8. The Committees suggested a systematic tiered approach to initial toxicological studies with nanomaterials. Given the paucity of toxicological data indicating which are the vulnerable cell types, and the likelihood that this will be variable depending on nanoparticle surface properties, *in-vitro* assessment should initially be directed towards those cell types shown to receive the highest nanoparticle dose in biodistribution studies (where this information is available). Because of the likely routes of exposure, such an approach would normally involve epithelial cells (e.g. respiratory and gastrointestinal tract) and macrophages (i.e. professional phagocytic cells) for assessment of cytotoxicity, adsorption/uptake, changes in oxidative status, release of mediators. Such studies would provide basic data that could be used for comparison between nanomaterials. This would be followed by a second tier of *in-vivo* studies using appropriate routes of exposure. It was noted that evidence of oral uptake of one type of single-walled carbon nanotube (SWCNT) had been identified.¹⁰ The Committees recognised the need for identifying ranges of standardised nanomaterials for these initial investigations to produce baseline information on

structural influences on toxicological responses (e.g. the impact of surface chemistry). It was acknowledged that the range of nanomaterials and uses would be very diverse. This approach can be summarised in the following figure.

Proposed approach to initial toxicological studies with nanomaterials



9. The Committees confirmed that there was no need to develop a new approach to risk assessment of nanomaterials but there was a clear need to provide hazard identification data on the widest possible range of nanomaterials. It was noted that in the absence of such data it was not possible to derive conclusions about the spectrum of toxicological effects which might be associated with nanomaterials. Thus it was noted that nanoparticles resistant to degradation could accumulate in secondary lysosomes, which in cells with a long survival such as neurones or hepatocytes might lead to chronic toxicity.

Additional comments from COM on mutagenicity evaluation.

10. The COM reviewed a number of publications where mutagenic effects *in vitro* had been specifically attributed to nanoparticulate titanium dioxide¹¹ and zinc oxide¹². However the COM noted inconsistency in the available mutagenicity data and in the information on the specification of the test materials used. It was therefore not able to conclude that any specific mutagenic activity had been documented which would not also be reported for studies using micrometre sized equivalents.

11. The COM considered that specific information on particle size was required to assess mutagenicity studies undertaken with nanomaterials. Thus, there was insufficient information on titanium dioxide to allow an assessment of the agglomeration/disagglomeration of particles in the vehicles used and it was not possible to conclude which particles had been tested. The COM agreed that it might be appropriate to support *in-vitro* mutagenicity tests with imaging data on particle sizes.

12. The Committees agreed that particle size was a generic factor which should be considered with all *in-vitro* testing of nanomaterials.

Additional comment from COC on carcinogenicity evaluation.

13. The Committees discussed whether SWCNTs and other carbon nanotubes might have carcinogenic potential analogous to fibres such as asbestos. Some recent information from the SOT abstracts using gold labelled SWCNT had demonstrated that some of these fibres may evade macrophage engulfment, although granuloma formation was still reported. It was considered they would not reach the mesothelium. The COC considered that more information (including detailed structural data, and absorption and cellular response in macrophages) was required on a range of single- and double-walled carbon nanotubes before any definite conclusions could be reached.

Epidemiological aspects of exposure to nanomaterials.

14. The Committees noted that there were no published epidemiological studies of nanomaterials available. They also noted that the Royal Society report had highlighted problems in the detection of nanoparticles. It was agreed that estimating human exposure to nanoparticles would be exceptionally difficult particularly where there was exposure to a range of both nanometre-sized and micrometre-sized particles. Similarly, assessment of the toxicity would need to distinguish effects arising from the nanoparticle form and those due to chemical composition. HSE have confirmed that the Health and Safety Laboratory (HSL) in Buxton is working with the US National Institute for Occupational Safety and Health (NIOSH) to develop techniques to carry out such monitoring in the future.

Concluding remarks

15. The Committees noted that the current review did not include information on mixtures of nanoparticles such as in environmental air pollution. Members considered that information from environmental epidemiology and volunteer studies of nanomaterials, predominantly from the field of air pollution research, might be informative in identifying end points for initial screening and possible hazards. It was suggested that liaison with other relevant expert groups such as the Committee on the Medical Effects of Air Pollutants (COMEAP) would be valuable. In addition information on medical applications of nanoparticles might be important to the COT discussions. Such information might be potentially relevant with regard to information on structure activity. The secretariat was asked to liaise with the Medicines and Healthcare products Regulatory Agency (MHRA).

16. The Committees reached the following overall conclusions:

i) We note that there is the potential for a wide range of nanomaterials to be produced by many different methods and that there is also the potential that they may be used for many different purposes. Two safety concerns arise: firstly, the intrinsic toxicity of the nanomaterial itself and secondly, the fact that products with potential for widespread human exposure (e.g. paints) may be delivered in future using nanotechnology.

ii) We have proposed a systematic tiered approach for initial toxicological studies on novel nanomaterials based on *in-vitro* screening of selected materials supported by biodistribution studies to aid in the identification of cell types for study, followed by appropriate *in-vivo* testing.

iii) We believe from the available toxicological data that current approaches to risk assessment should be appropriate for nanomaterials. However there are limited toxicological data on nanomaterials at present and we consider it is necessary to keep a watching brief of the developing area of nanomaterial toxicology.

iv) We note the difficulties in determining exposures to nanomaterials but consider this to be a high priority for further research so that appropriate risk assessments can be undertaken.

v) We suggest close collaboration and exchange of information between COT/COC/COM and COMEAP and the MHRA so that information on environmental air pollution and human medicines can be included in further reviews of nanomaterials. Such information may help to identify potential areas of hazard and risk assessment for nanomaterials used in manufactured products.

vi) We consider this subject should be subject to regular reviews by COT/COC/COM.

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Minutes of 2004 COT horizon scanning:

http://www.food.gov.uk/science/ouradvisors/toxicity/cotmeets/cot_2004/169681/cotmin2february2004

COM/COC horizon scanning papers for 2004:
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<http://www.advisorybodies.doh.gov.uk/pdfs/cc0432.pdf>)