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CC/05/18

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD,
CONSUMER PRODUCTS AND THE ENVIRONMENT. (COC)**

DRAFT WORKING PAPER ON NANOMATERIAL TOXICOLOGY.

Introduction.

1. The risk assessment of nanomaterials has been identified by COT/COC/COM as an area of interest during horizon scanning discussions for 2004. The Committee's interest in this area was prompted by the publication of the royal society review of nanotechnology. (<http://www.nanotec.org.uk/>) The appended documents have been drafted to provide baseline toxicology information for all three committees. These comprise; The objective is to collect initial views from the COC (21 April), COM (26 May (deferred to October 2005)) and COT (12 July) and draft a short statement. The timescale is to complete the statement by the end of 2005.
2. The COC discussed the available toxicology on nanomaterials at its April 2005 meeting. The COT discussed at the July and October 2005 meetings. A draft working paper was considered at the COM October meeting and the COT October meeting.
3. The COC is asked to comment on the enclosed draft working paper, which present draft amendments suggested by COT and COM. Members are specifically asked to consider para 11 which is based on comments from Dr Carthew and Professor Boobis at the July COT meeting
4. It is hoped this will be published on COT/COC/Com internet sites as a short baseline information statement.

Secretariat October 2005

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

JOINT WORKING PAPER 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 and 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 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 and its sister committees on carcinogenicity (COC) and mutagenicity (COM) carry out regular horizon scanning exercises as part of their annual remit (see appended internet links at the end of this statement). 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 abstracts from the US Society of Toxicology 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.

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4. ~~Conventionally~~ Nanomaterials are defined in the Royal Society report as having one dimension less than 100 nanometres (nm) or 0.1 micrometre (μm).² 'The Committees agreed that this should not be viewed as a rigid definition. There are two basic approaches to generating novel nanomaterials. ~~T~~ ~~;~~ ~~top down~~' technologies using machining and etching methods that create particulates which are usually found in micrometer sizes, but can also be produced in nanometre dimensions ~~(an example is nanometre sized zinc oxide used in certain cosmetic preparations);~~ Examples include engineered surfaces, and surface coatings (e.g fuel cells and catalysts) and microcrystalline materials (potential uses are in textiles, cosmetics, and paints). The Committees noted that nanoparticles were also produced during combustion, food cooking and from vehicle exhausts. ~~and B~~ ~~bottom-up~~' nanotechnologies which represent production of nanomaterials from individual molecules and are novel, e.g. carbon nanotubes and nanofoam, nanodots and fullerenes. Some possible examples of bottom up nanomaterials ~~Nanomaterials can be subdivided as~~ are shown below.

	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-biodegradable			Lightweight, spongy solid, can act as semiconductor. Magnetic property

5. Nanomaterials have ~~a~~ high proportion of their total atoms will be at the ~~at the~~ particle surface, ~~which behave like individual atoms,~~ 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

Potential approach to hazard screening of nanomaterials

6. The Committees agreed the objective of the review was to provide a baseline statement on the available information on nanomaterials toxicology. There are considerable limitations in the number of materials and extent of toxicology data available. In addition it is expected there will be considerable

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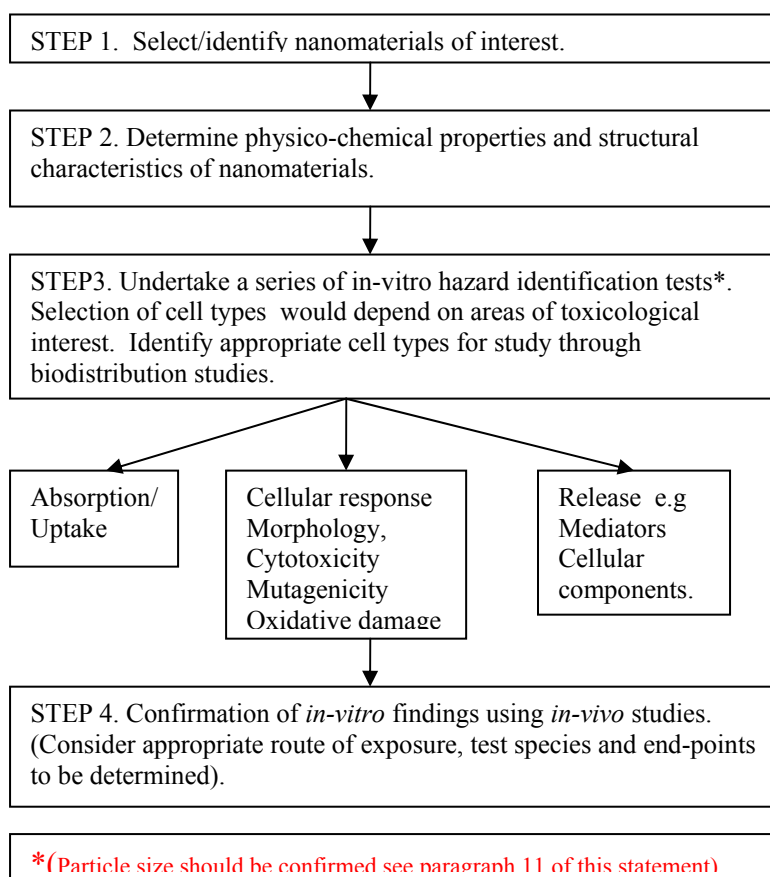
growth in the number of nanomaterials produced industrially and their potential commercial applications. There is also virtually no information on potential human exposure resulting from environmental exposure. To some extent this reflected the limited commercial applications to date (excluding medicinal/cosmetic 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 micrometer sized and nanometre sized equivalent materials. The Committees noted that there is limited information on both types of nanomaterials, particularly the novel nanoparticles.

7. Possible ~~mechanisms of action~~ 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 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 felt there was scope for considerable research into the ~~mechanisms of 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 hazard identification for all types of nanomaterials. This would involve *in-vitro* studies using predominantly epithelial cells (respiratory, gastrointestinal tract) and macrophages for cytotoxicity, adsorption/uptake, changes in oxidative status, release of mediators. Such studies would provide basic ~~mechanistic hazard identification~~ data that could be used for comparison ~~between nanomaterials and particles~~. 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.

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Scheme for initial hazard identification 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 of 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 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 the inconsistency in the available mutagenicity data and information on the specification of the test materials

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used and was therefore not able to conclude that any specific mutagenic activity had been documented which would not also be reported for studies using micrometer sized equivalents.

11. The COM considered that specific information on particle size was required to assess mutagenicity studies undertaken with nanomaterials. Thus the available information on titanium dioxide did not allow an assessment of the agglomeration/disagglomeration of particles in the vehicles used and it was not possible to conclude what 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 sizing was a generic factor which should be considered with all *in-vitro* testing of nanomaterials.

Additional comment from COC on carcinogenicity evaluation.

134. 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 but did result in~~ 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.

142. The Committees noted that there were no published epidemiological studies of nanomaterials available. The Committees noted that problems in the detection of nanoparticles had been highlighted in the Royal Society report. One suggestion was that incorporation of fluorophores into nanoparticle manufacture would help address these problems. 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 micrometer-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 Sheffield 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

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153. 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, volunteer studies of nanomaterials, predominantly air pollution 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 were asked to liaise with MHRA.

14. The Committees reached the following overall conclusions:

i) We note the diversity and potential for manufacture and use of a wide range of nanomaterials produced by machining of currently available materials and by manufacture of novel nanostructure. We note the paucity of available toxicological data on nanomaterials and consider there is a clear need for a systematic approach to generating basic hazard identification data on these materials. We have suggested a **potential scheme approach for comparison between nanomaterials and for prioritisation** based on *in-vitro* screening of selected materials followed by appropriate *in-vivo* testing **supported by biodistribution studies to aid in identification of cell types for study..**

ii) We consider, from the available toxicological data, that current approaches to risk assessment should be acceptable for nanomaterials.

iii) 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.

iv) We suggest close collaboration and exchange of information between COT/COC/COM and COMEAP and the MHRA so that information 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.

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

2005

October ~~August~~

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References

1. UK Government (2003). The Governments Response to Better Regulation Task Force's report on Scientific Research: Innovation with Controls. <http://www.brtf.gov.uk/docs/pdf/scienceresponse.pdf>
2. The Royal Society and Royal Academy of Engineering (2004) Nanoscience and nanotechnologies: Opportunities and Uncertainties, published 29 July 2004, <http://www.nanotec.org.uk/finalReport.htm>
3. HM Government in consultation with devolved administrations (2005). Response to The Royal Society and Royal Academy of Engineering report "Nanoscience and nanotechnologies: Opportunities and Uncertainties", http://www.ost.gov.uk/policy/issues/nanotech_final.pdf
4. COT (2005). Overview of nanomaterial toxicology. <http://www.food.gov.uk/multimedia/pdfs/TOX-2005-19.pdf>
5. COC (2005). Overview of nanomaterial toxicology. <http://www.advisorybodies.doh.gov.uk/pdfs/cc055.pdf>
6. COM (2005). Overview of nanomaterial toxicology Consideration of mutagenicity data. <http://www.advisorybodies.doh.gov.uk/pdfs/mut0515.pdf>
7. HSE (2004) Health effects of particles produced for nanotechnologies, EH75/6. <http://www.hse.gov.uk/horizons/nanotech/index.htm>
8. Society of Toxicology (2005) 44th Annual Meeting to be held March 6–10, 2005, in New Orleans, Louisiana. Abstracts. Published in The Toxicologist, volume 84, march 2005.
9. Seaton, A., MacNee, W., Donaldson, K. and Godden, D. (1995) Particulate air pollution and acute health effects. *The Lancet* 345, 176-178.
10. Wang H, Wang J, Deng X, Sun H, Shi Z, Gu Z, Liu Y and Zhao Y. Biodistribution of carbon single-wall carbon nanotubes in mice.
11. Rahman Q, Lohani M, Dopp E, Pemsel H, Jonas KL, Weiss DG and Schiffmann D.(2002) Evidence that ultrafine titanium dioxide induces micronuclei and apoptosis in Syrian hamster embryo fibroblasts. *Environmental Health perspectives*, 110, 797-800.
12. SCCNFP (2003). Final evaluation and opinion on zinc oxide. SCCNFP/0649/03 final.

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(COM/ COC horizon scanning papers for 2004.

<http://www.advisorybodies.doh.gov.uk/pdfs/MUT0422.pdf>

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