COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COT ADDENDUM TO JOINT STATEMENT OF THE COMMITTEES ON TOXICITY, MUTAGENICITY AND CARCINOGENICITY ON NANOMATERIAL TOXICOLOGY

Background

1. In December 2005 the Committees on the Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COT, COC and COM) published a joint statement on nanomaterial toxicology http://www.food.gov.uk/multimedia/pdfs/cotstatements2005nanomats.pdf.

2. The objective was to provide a baseline statement on the available information on nanomaterials toxicology. The Committees suggested a systematic tiered approach to initial toxicological studies with nanomaterials. The Committees stated 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.

3. In the concluding remarks the COT indicated additional information on medical applications of nanoparticles might be important to their discussions and might be potentially relevant with regard to information on structure activity.

MHRA review.

4. Following discussions between the secretariat and Medicines and Healthcare products Regulatory Agency (MHRA), the MHRA produced a review of information on the toxicology of nanoparticles used in healthcare. This MHRA review aimed to identify whether healthcare nanoparticles introduced any new toxic hazards and was based on published literature from the last five years supplemented by additional specific product information. The review excluded healthcare products where the administered product is a single large molecule or entity that just happens to fall in the nanoparticulate scale such as pro-drugs,

biological macromolecules and viral transfection agents. Many publications involved *in vitro* proof of principle with incidental cytotoxicity information. The review can be found at http://www.food.gov.uk/multimedia/pdfs/TOX-2006-28.pdf.

COT discussion.

5. Based on this comprehensive review, the toxicological database to date was considered to be still inadequate to indicate whether nanoparticles have a specific form of toxicity. The apparent emphasis on an initial wide ranging *in vitro* investigation in nanotoxicology testing strategies might represent a misunderstanding of the role of *in vitro* data since animal studies remained the key hazard identification studies. The role of *in vitro* testing is as part of a tiered approach to decision making and not a means of detecting toxicity endpoints other than genotoxicity hazards.

6. Having considered the new data on healthcare nanoparticles, there were limited data on extrapolation from animals to humans and therefore the implications of such extrapolation and use of standard uncertainty factors would need further consideration as data emerged. Bioavailability and biodistribution studies have a critical role in evaluation of nanoparticles and such information is not obtained from *in vitro* studies. Common mechanisms of toxicity, for example, oxidative stress might also provide a method for prioritisation of those nanoparticles that need further testing.

7. The approach to biodegradable and non-biodegradable nanoparticles might need to be different. There is no evidence that biodegradable nanoparticles have toxicity intrinsic to their nanoparticulate state. In contrast, the evidence indicates that non-biodegradable nanoparticles can cause cell death due to their physical nature by accumulating and overloading lysosomes. Although there was an extremely limited database some studies on nanoparticles had shown evidence of potential shape-specific biological properties.

8. The information reviewed indicated there was a need to consider formulation effects which can affect surface charge and particle size and influence the resulting toxicity. Product specific assessments would be needed as well as clarity on the formulations tested. The COT was informed that this could raise difficulties for evaluating nanoparticles in cosmetics since current EU legislation does not allow *in vivo* testing on cosmetic formulations.

9. The mechanisms of toxicity seen with healthcare nanoparticles were not unique. There is a need for sufficiently sensitive endpoints to identify effects which had predictive validity for potential adverse effects in humans.

10. Conventional toxicological assessment should be sufficient to identify toxic hazards from biodegradable healthcare nanoparticles. However, it was

important to ensure study designs were appropriate to the nanoparticle under investigation. Whilst the standard toxicological test batteries would detect possible effects from healthcare nanoparticles, there was as yet, insufficient information to exclude the possibility of effects not detectable by these methods. The COT was not currently aware of such effects being reported.

11. For pharmaceuticals it has been shown that incorporation into nanoparticle formulations can greatly influence the biodistribution (and hence toxicity) of included chemicals. Indeed the intention behind many such formulations is to facilitate drug delivery across tissue barriers. There is little evidence that the biodistribution of other chemicals not physically included in the original formulations, but accidentally present in the body at the same time as the nanoparticles, can be so influenced. However there is at least a theoretical possibility that freshly generated nanoparticles with reactive surfaces could significantly bind and alter the biodistribution of other xenobiotics. Such effects would not represent nanoparticle toxicity per se, but would represent a consequence of co-exposure.

12. The COT reached the following conclusions in addition to those in paragraph 12 of the joint statement on nanomaterial toxicology http://www.food.gov.uk/multimedia/pdfs/cotstatements2005nanomats.pdf

    I. We wish to emphasise that the role of *in vitro* testing is part of a tiered approach to decision making and not a means of detecting toxicity endpoints other than genotoxicity.

    II. We concluded that the approach to the risk assessment of biodegradable and non-biodegradable nanoparticles should be different, since the available evidence indicates that non-biodegradable nanoparticles can cause cell death due to their physical interaction with cells. In contrast, biodegradable nanoparticles are less likely to have toxicity intrinsic to their nanoparticulate state.

    III. There is some limited evidence available to indicate that formulation, i.e. the matrix in which the nanomaterial is present, can affect surface charge and particle size and influence the resulting toxicity. Therefore we conclude that available evidence on formulation effects on toxicity of nanoparticles should be monitored.

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