New and Emerging Issues 2006
Occupational Health Aspects of Nanotechnologies

ANNEX 2: Relevant extract of minutes of WATCH meeting January 2005

3.4	***Discussion on HSE's hazard assessment (Annex 1)*** The Chair then directed the discussion to the specific action points, beginning with Action Point [a]: WATCH is asked to "*endorse or suggest any necessary modifications to HSE's assessment of the current state of knowledge about the human health hazards of nanoparticles*".
3.5	<u>*Agglomeration and dose-response*</u> WATCH first considered the question of agglomeration of nanoparticles. A WATCH Member noted that the extent to which agglomeration occurs is inversely related to particle size and the rate of agglomeration increases with increasing particle concentration. He asked if this could result in a non-linear relationship between airborne nanoparticle concentration and toxicity? In response, another Member cited experimental work by Oberdorster *et al* (1992), which suggested that toxicity is diminished as a result of particle agglomeration. This Member also pointed out that agglomeration is accompanied by a reduction in the total amount of free radical activity on the particle surface and that this reduction might also contribute to amelioration in toxicity. He commented however, that in experimental work, aggregated nanoparticles consistently elicit greater toxicity on a mass basis than larger, singlet particles, i.e. agglomeration might somewhat reduce toxicity but that even with agglomeration, an effect is evident that is more related to the extensive surface area of an agglomerate than to its mass. In this context, another Member commented that a distinction should be made, when appropriate, between observations of toxicity from *in vitro* compared with *in vivo* studies. One had to be careful not to extrapolate too readily the consequences of short-term contact with cells in culture to long-term consequences of whole-animal/human exposure.
3.6	<u>*Susceptible groups*</u> A WATCH Member asked if any particular population groups were likely to be particularly susceptible to any health effects associated with exposure to nanoparticles? It was pointed out that from our understanding of air pollution episodes, exposure to PM_{10} (particulate matter $< 10\ \mu m$) is associated with adverse health outcomes in susceptible populations e.g. those with pre-existing asthma or cardiovascular disease. It has been suggested that these adverse health outcomes are especially related to the nanoparticulate component of PM_{10}. If so, then these same population groups could also be particularly susceptible to any adverse health effects associated with exposure to novel nanoparticles. Another factor to consider is the presence of pre-existing airways disease, as this would affect particle deposition within the respiratory tract; so, for example, individuals with chronic obstructive pulmonary disease or other airways disease could respond differently to inhaled particles because of differences in the pattern of particle deposition in the airways. The Chair suggested that the points made in relation to susceptible populations could be borne in mind in HSE's continuously evolving view of the potential threat to human health posed by novel nanoparticles.
3.7	<u>*Viruses as nanoparticles*</u> A WATCH Member asked if any useful information could be obtained from existing knowledge on behaviours of viruses within the body, as viruses could be regarded as nanoparticles. In response, it was noted that information on the transfer of viruses via the olfactory nerve had been cited in support of very recent work that looked at axonal translocation of nanoparticles that deposited in the nasal passages.
3.8	<u>*Potential absorption and systemic toxicity*</u> A different WATCH Member noted that the potential systemic toxicity of nanoparticles was an important consideration, given that studies of pharmaceuticals had shown that even for poorly

	soluble substances, rendering them "nano-sized" resulted in a massive increase in bioavailability following oral administration. He suggested that this increase in absorption and bioavailability may apply to other exposure routes.
3.9	*'Dose' or 'potency' as the key influence on toxicity?* The question was then raised whether the differences in observed toxicity between nanoparticles and their micrometre counterparts were simply a function of dose (i.e. amount, expressed as the appropriate metric) or represented a change in toxicological potency (i.e. activity)? A response was offered that results from both *in vitro* and animal models can be explained by a two-stage model that incorporates both surface area and surface activity as important parameters in the expression of toxicity. The comment was made that the potential for apparently 'low-toxicity' micrometre-sized particles to express toxicity when in the nanometre range should be clearly emphasised.
3.10	Another WATCH Member pointed out that whilst surface area is an important determinant of toxicity, other factors such as chemical activity are also important. In addition, it is not clear whether the apparent relationship between particle surface area and toxicity will hold for all materials.
3.11	*Additional useful data?* The Chair then asked Members if they were aware of any additional useful hazard information that had not been included in the review.
3.12	One Member commented that very few human data are included, for example, from the wealth of epidemiological studies looking at environmental air pollution episodes, and that these may be informative. HSE responded that these data had been considered, but a detailed account of them was omitted from the document because it was not possible to separate out the contribution made by the nanoparticulate component of particulate air pollution to the observed health outcomes; this point was made in the review. Nevertheless, HSE intended to keep abreast of the literature to which WATCH had referred to inform its evolving view of the potential threat to human health posed by nanoparticles arising from nanotechnologies.
3.13	*Skin absorption* Another Member raised the issue of skin absorption of nanoparticles. It was noted that there was a discontinuity in this respect between the hazard assessment document and the exposure assessment; the former concludes definitively that skin absorption is negligible, certainly for poorly soluble nanoparticles, whereas the exposure assessment suggests that uptake via the skin may be an important route of exposure. It was agreed that given the paucity of informative data, a definitive conclusion on the skin absorption potential of nanoparticles could not yet be reached. HSE would therefore revise its position on this issue within its evolving view on the potential threat to human health posed by novel nanoparticles.
3.14	*GI tract absorption* The issue of absorption through the gastrointestinal (GI) tract was also raised. It was noted that this aspect had not been addressed in the hazard assessment. However, given that a significant proportion of particles cleared from the lung will reach the GI tract via the mucociliary escalator, this is an important exposure route. In this context, the comments made previously in relation to potentially useful data from studies of nanoparticulate pharmaceuticals were relevant.
3.15	*General applicability of hazard assessment* One WATCH Member commented that the hazard assessment focuses on studies of conventional chemical structures that have been produced at the nanoscale, rather than on novel nanomaterials, because of the lack of toxicological data for the latter. However, he argued that it was not necessarily appropriate to extend the conclusions reached from investigations of the materials studied to all particles potentially arising in the future from nanotechnologies.
3.16	*Deposition* One WATCH Member asked for clarification in the Annex, to indicate what proportion of inhaled

	submicron particles is deposited in the respiratory tract. This aspect is important as it will affect the numbers of particles, and thus the particle surface area, that deposit within the respiratory tract. On checking this point after the meeting, HSE notes that total deposition can be inferred from Figure 2 of the Annex. The diagram shows the total deposition of particles within the airways, from which it can be inferred what percentage of particles is not deposited.
3.17	<u>*Conclusions on hazard assessment*</u> Overall, considering Action Point [a] of the cover paper: • **WATCH agreed that the HSE's hazard assessment represented an accurate appraisal of the current extent of knowledge on nanoparticles. However, HSE would take account of the comments made by WATCH in the ongoing process of keeping abreast of the potential human health hazards of novel nanoparticles.**
3.18	***Discussion of occupational exposure to nanoparticles*** The Chair then asked members to consider Action Point [b] of the cover paper which asked WATCH to "*take a position on what exposure metric(s) should be pursued in relation to assessing workplace exposure to, and control of nanoparticles (e.g. mass, surface area, particle number)*" (Annex 2 of the package).
3.19	A Member asked if there were any methods for measurement of surface area that were suitable for use in the workplace. Another Member explained that current methods involved sophisticated and expensive techniques that were not readily applicable outside the laboratory situation. He added that indirect methods for estimating surface area from other measurements, such as particle number, are relatively easy in comparison, but consequent extrapolation cannot take account of particle agglomeration; current particle counting techniques will count an agglomeration of nanoparticles (of perhaps up to 500 particles) as a single particle, so can give misleading results. It was necessary to use a combination of information on surface area, particle number and particle mass to estimate exposure to nanoparticles.
3.20	An HSL representative indicated that HSL has a project underway to look at the inter-relationships between particle mass, number and surface area. Although there is a device for measuring surface area, it is not a personal monitor. However, HSL intends to trial this device in factories manufacturing novel nanoparticles.
3.21	Clarification of the figures in Table 5.7 on page 38 of Annex 2 was sought. A WATCH Member noted that this table reported a series of measurements expressed as particle number (Wake, 2001) whereas the remaining entries in the table referred to mass concentration. The WATCH Member noted that the numbers reported seemed low compared with background environmental particulate levels, which he understood were of the order of 10 000-20 000 particles/cc air. He asked how the measurements by Wake (2001) had been made. HSE (HSL) explained the techniques that had been used, and commented that although the numbers seemed low, it was known to be the case that particle measurements taken inside a factory could be lower than the outside levels, a reflection of the control systems in place.
3.22	HSE pointed out that DTI has allocated a great deal of research money to develop appropriate measurement methodologies, and so in the context of considering what might be the most appropriate exposure metric to pursue, WATCH need not restrict its considerations to currently available techniques.
3.23	One WATCH Member proposed that the key dose metric is surface area. Another Member added that there are two issues to consider in relation to deriving an appropriate dose metric: one is the underlying mechanism of toxicity and the other is the practicality in relation to worker protection. He noted the significant challenge of developing practical methods to measure surface area in the workplace and so felt that this aspect requires the development of reasonably reliable surrogates or indirect methods. Another Member suggested that perhaps useful lessons in risk management could be learned from experience with welding fume. If it could be ascertained that nanoparticles contribute substantially to the toxicity of welding fume, then knowledge of the standards to which it is deemed necessary to control welding fume may lead to the development of a surrogate method for assessing the appropriate standard of control for nanoparticle exposure more generally. A different Member responded that experimental work had been done to establish the underlying basis for welding fume toxicity.

	He felt that this had shown the toxicity to be attributable to the transition metal content of the fume rather than its nanoparticulate nature.
3.24	A number of WATCH Members then voiced the view that it is inappropriate to try to establish a single dose metric that is suitable for all nanoparticles and situations, and that a case-by-case approach is needed. So, for example, measurement of surface area may be the best dose metric for nanoparticles of inherently low cytotoxicity, but not necessarily for all nanoparticles. Another Member added that this debate on exposure had focused on inhalation, but the need to measure exposure via other routes should also be considered, as these other routes might also prove to be important.
3.25	With regard to Action Point [b], the Chair summarised and verified with WATCH the position that had been arrived at: • **The ability to measure surface area, either directly or indirectly was important. However, it was also necessary to take a case-by-case approach to measurement, as the most appropriate metric for one type of nanoparticle may not be appropriate for another. Finally, it was noted that consideration of routes of exposure other than inhalation was important in undertaking any worker risk assessment.**