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Nano-technology and nano-toxicology

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Rapid developments in nano-technology are likely to confer significant benefits on mankind. But, as with perhaps all new technologies, these benefits are likely to be accompanied by risks, perhaps by new risks. Nano-toxicology is developing in parallel with nano-technology and seeks to define the hazards and risks associated with nano-materials: only when risks have been identified they can be controlled. This article discusses the reasons for concern about the potential effects on health of exposure to nano-materials and relates these to the evidence of the effects on health of the ambient aerosol. A number of hypotheses are proposed and the dangers of adopting unsubstantiated hypotheses are stressed. Nano-toxicology presents many challenges and will need substantial financial support if it is to develop at a rate sufficient to cope with developments in nano-technology.

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Nano-technology has a strong claim to be regarded as the first important advance in technology of the third millennium. This is a remarkable thought: who would care to predict what other advances might occur during the coming thousand years? Science fiction might be as good a guide as science itself in predicting such developments; for those who dream of space elevators constructed of woven graphene produced on asteroids by self replicating machines, the trilogy Red Mars, Green Mars and Blue Mars by Kim Stanley Robinson is strongly recommended (1). Those concerned about the possible effects on mankind of gene therapy will also find this book interesting. But this is science fiction, what of science fact? Well, even a slight acquaintance with the nano-technology literature suggests that the facts are fast approaching the predictions of fiction. From the packaging of 'smart drugs' so that they can reach the central nervous system or be directed precisely towards tumour cells (2), to self cleaning glass; from nano-silver being incorporated into odour-eating socks to the development of stealth fighters; from artificial muscles to desalination plants; from safer nuclear power to better clinical diagnostics (3), there is hardly a field of human endeavour in which nano-technology has not been said to be likely to play an important part. And the rate of development of the field is staggering: well informed experts speak of a trillion dollar industry appearing within just a few years (4). The use of nano-materials seems to be likely to become universal; little wonder, then, that concerns have been expressed about the possible effects of exposure to these materials. These include the very unlikely, 'grey goo' spreading across the land and the spread of self replicating, virus-simulating, nanobots, and the less unlikely but by no means likely damage to health and to ecosystems. The field is expanding in as many directions as might well be imagined; nano-toxicology is one of these directions. A Pub Med search on the word nanoparticle produced more than 55,000 references: scanning the list reveals many titles that might well have appeared only a few years ago in science fiction. Nano-toxicology is also developing rapidly and the funding base, though weak only a few years ago is now strong though far from what might be needed. Inhalation toxicology is experiencing a pleasurable renaissance: monographs are appearing (4–6), new journals have been launched (Journal of Nanotoxicology, Nanomedicine, Particle and Fibre Toxicology, Nature nanotechnology, Journal of Nanoparticle Research, Nanotoxicology) and papers revealing the effects or lack of effects of nano-particles are being published almost daily. A number of wide ranging reviews have been published (7–11). The 2005 review by Oberdörster et al. (12) is outstanding and should be studied by all interested in this field. Concern has focused on engineered nano-particles. Comparatively little attention has been focused on the potential hazards of nano-particles used for medical diagnosis or on nano-preparations of drugs: the likelihood of there being general exposure to these preparations is, rightly, judged to be low.

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Reasons for concern

Why so much concern? The fundamental reason is simple: when materials are presented as nano-materials they may behave physically, chemically and toxicologically in ways that cannot be predicted by study of the parent material. Gold is an inert metal; nano-particles of gold less than 10 nm in diameter burst into flames on contact with oxygen. Even if less unexpected and dramatic effects occur when nano-particles come into contact with tissues the toxicological activities of materials in nano-form may be quantitatively very different from those of the parent materials. Titanium dioxide, the standby negative control of many inhalation toxicologists, is much more active, in terms of producing an inflammatory response in the lung, when presented as 20 nm diameter particles than as 250 nm diameter particles (12). This very important finding has been disputed by Warheit et al. (13): their paper should be studied for a possible explanation (based on an examination of the crystal structure of the materials used) for this discrepancy of findings. The worst case position is clear: any material might be toxicologically active, or more active, in an unpredictable way (quantitatively and more worryingly, qualitatively) when presented to the body in nano-form. Thus every material that might be presented to the body, deliberately or accidentally, in nano-form needs to be examined, in nano-form, for its toxicological effects. Essentially: toxicologists can start again. In fact, the worst case might be worse than this: not only should all materials that might be presented in nano-form be studied again but they should be studied when attached to the surface of, or incorporated into, other materials in nano-form. The interactions between the carried and the carrier might define the toxicological properties of the combination. And if that were not startling enough, the same can be said for eco-toxicological effects.

A second reason for concern about the possible effects on health of nano-particles lies in the air pollution field. It is accepted that exposure to the ambient aerosol damages health. This effect has been explored in terms of the relationships between day to day variations in mass concentrations of particles and daily counts of deaths, hospital admissions and so on. In addition, long term exposure to ambient particles monitored as PM2.5 (the mass per cubic metre of particles generally less than 2.5 μm in diameter) has been shown to be associated with increased risks of death from cardiovascular disease and lung cancer. That deaths from cardiovascular disease were associated with ambient particles was news in the 1990s and led Seaton and his colleagues to propose that ultrafine particles might be the cause of this effect (14). They argued that the mass dose of particles might be misleading us (it is very small because ambient concentrations of particles are low, annual average PM2.5 in England is of the order of 10 $\mu g/m^3$) and that very small particles that contribute little to the mass but a great deal to the number, of particles per unit volume of air, might by crossing the alveolar air-tissue barrier triggering effects that lead to a worsening of cardiovascular disease. This was a startling idea: to some it suggested that the wrong particles were being monitored; to others it suggested a new field of research. Support for the idea came from the work of Peters and colleagues (15) who showed that blood viscosity in patients with CV disease tracked with the number concentration of ambient particles: See Delfino et al. (16), for further references in this area. The possible prothrombotic effects of nanoparticles have been explored by Geys et al. (17). These authors showed that Quantum Dots could, at high intravenous doses, induce pulmonary vascular thrombosis in mice. Platelet aggregation and activation are thought to underlie this effect. Seminal studies of nano-particles by Oberdörster and his colleagues have provided further support (18–21). A surge of research on ambient particles followed.

Possible explanations for the effects of ambient particles

A number of theories to explain how ambient particles might exert their effects have been put forward: the generation of oxidative free radicals has proved a durable suggestion; that transition metals might play a part in this has received much support. It is interesting, in this context, to note that Carbon Black appears to be able to induce formation of oxidative free radicals without the involvement of transition metals (22). It may be that ultrafine particles act by delivering transition metals to the alveolar surface, the metals then act as catalysts for reactions that generate oxidative free radicals which can damage cell membranes and trigger chain reactions. By acting as catalysts and not as conventional reactants in these reactions, transition metals might exert an effect far beyond that which might have been predicted on the basis of the mass dose of metals delivered to the lung. In fact the mass dose of metals will, inevitably, be very small: they make up only a fraction of the mass dose of the particles and that dose is, itself, small. By triggering chain reactions the metals might, again, cause effects out of proportion to their mass. That the ultrafine particles might cross into the blood and be disseminated to other organs and there produce a wide range of effects, has been suggested (see below). All too quickly the hypothesis expanded towards explaining everything and has become difficult to test. Diagrams showing the possible dispersion of inhaled, ingested or dermally absorbed nano-articles throughout the body have become commonplace in reviews of this subject (12). Such diagrams, inevitably at this stage, lack information on the quantitative importance of the various pathways indicated. What percentage of inhaled particles crosses from the alveoli

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to the blood? What percentage enters the brain via the olfactory nerves? How are nano-particles excreted? Are they sequestrated at sites in the body, for example in the cells of the reticulo-endothelial system? What of species differences? What of differences from one nano-particle to another or, even, from one sample of one type of nano-particle to another? Some of these questions are discussed below.

Definitions

Nano-toxicology grew from studies of ultrafine particles. It might be useful, now, to define ultrafine and nano-particles. The term 'ultrafine' is used by many air pollution scientists to denote particle of less than 100 nm diameter. The term 'nano-particle' has rather overtaken the term 'ultrafine particle' and is now used to describe material presented in a form such that at least one dimension of the unit material is of less than 100 nm. Thus nano-dots, nano-spheres, nano-plates, nano-tubes, nano-wires are all nano-materials or nano-particles. Nano-tubes have attracted much attention. These graphene structures may be single or multi-walled and may carry contaminating metals (derived from the production process) on their surfaces. They are notable strong and are commonly many times longer than they are broad. Tough, long, narrow fibres that are deposited in the alveoli: new asbestos? Perhaps so: certainly the work of Poland et al., Tagaki et al. and Mercer et al. (23–25) suggests that exposure to such materials should be controlled.

The peculiar challenge of nano-toxicology

Toxicological testing of every material that might be presented to the body, deliberately or accidentally, in nano-form is infeasible; developing a capacity to predict the effects of nano-materials is essential. On this most toxicologists agree; developing the theory, a general theory of nano-particle toxicology, is more difficult. But a similar problem was faced more than thirty years ago in the fibre-toxicology field and the characteristics of fibres that should be causes for concern were defined. These included the ratio of fibre length to breadth, the durability of fibres in the lung and the level of exposure. These have been found to be reliable guides. Developing similar, albeit no doubt more complex, guides for predicting the toxicological effects of nano-particles is perhaps the key challenge of nano-toxicology.

All toxicologists would agree that defining the material to be studied is important. Often this is not too difficult: a study of the toxicology of potassium cyanide administered intravenously would require that the purity of the sample of salt was known. Complete purity is impossible but the very minor impurities in potassium cyanide bought from a reputable supplier are unlikely to make much difference to the results of the study. The level of purity of the preparation used would, of course, be reported. Consider, now, the problems of dealing with a sample of carbon nano-tubes. These might be received from the supplier in a bottle: the material would look much like soot. The material is insoluble in water. Determining the physical characteristics of the material would be a challenge; a challenge far beyond the abilities or, at least, the resources of most toxicologists. A group of distinguished workers in the field have defined 17 physico-chemical characteristics which might be important to determine before studying such material (26). These include particle (in this case fibre) size, shape, surface area per unit mass and also porosity, surface contamination and surface charge in suspension and in bio-fluid surrogates. Fubini et al. have stressed similar features of nano-particles with an emphasis on possible genotoxic effects (27). Rather worryingly the history of the material is also important. This is a very real problem: if the material changes with storage then the toxicologist will have additional problems. Heraclitus said that one could not step twice into the same river; Cratylus famously capped this by saying that one could not step once into the same river. The same might almost be said of a sample of nano-material: we can discover something of the specific material provided and studied the way described, but can we use this information in a predictive sense and develop from it our general theory?

Difficulties in characterising the material to be studied become more taxing when we move away from the stock bottle, though difficult enough there, to the animal. If exposure by inhalation is intended then some means of aerosolising the particles will be needed. At present there are few devices that will produce a satisfactory aerosol of carbon nano-tubes: one such device which has been developed in the US is currently being built for the National Nano-toxicology Research Centre at Chilton in England. The aerosol may change in the period between generation and inhalation: agglomeration (weak adhesion between primary particles) or aggregation (firm adhesion) may occur and, of course the aerosol will have to be monitored. Monitoring the aerosol for distribution of particle size is costly and requires a familiarity with aerosol physics (28). Once inhaled the aerosol may undergo further changes on coming into contact with the lining fluid of the lung. Further aggregation or, as some have suggested, disaggregation may occur. The particles will hardly remain in their original state: coating with lipids and proteins is likely, perhaps inevitable. What the effects of such coatings may be is unknown; perhaps they aid penetration into cells, perhaps they increase the likelihood of uptake of particles by macrophages. The effects of charge on the acquisition of a coating and on the likelihood of the particles crossing cell membranes require study.

Creating a suspension of nano-particles in liquid is almost as demanding: anybody can add a gram or two of nano-particles to saline, sonicate it and inject a sample of the suspension into an animal. But determining the state of the particles in the suspension is far from easy. Aggregation is likely to occur and dispersants are commonly used to prevent this. The toxicological effects of these dispersants, not *per se* but in association with the particles, require study (29). This is difficult as one might not be able to study the effects of the particles without the dispersant though one can study the dispersant without the particles. And, of course, nano-particles cannot be made visible with a conventional light microscope: the limit of resolution (250 nm) prevents this. Instruments that rely on light scattering do allow resolution of a sort: rather as we see stars, as points of light rather than as structures (for example the moon) with defined edges and surface features. Labelling of nano-particles with fluorescent materials also allows them to be seen using a light microscope. Electron microscopy, of course, allows nano-particles to be seen but sampling of suspensions and tissues containing nano-particles for EM study brings its own problems.

Current work with radioactive nano-particles

These difficulties have led research workers to work with simpler systems. One successful approach has involved the production of nano-particles of Iridium 192 (^{192}Ir). This radio-isotope is an emitter of beta and gamma radiation with a half life of 74 days and can be monitored in tissue. Nano-particles can be produced by generating a high voltage spark across two iridium electrodes. Iridium labelled carbon nano-particles can be produced by substituting a carbon electrode for one of the iridium electrodes. The primary particles produced are of about 4 nm diameter but these soon aggregate to produce larger particles. The extent of aggregation can be controlled by adjusting the flow of inert gas through the system. Particles of 15 and 80 nm diameter have been used by Kreyling et al. (30). Iridium is a hard metal, few if any are harder, and effectively insoluble in body fluids even when presented in nano-form. Presentation in this form provides a large surface area per unit mass and is stern test of insolubility. What happens to these particles in the lung? It has been shown that they are cleared rapidly from the lung but, importantly, that they do not translocate efficiently into the blood stream. Kreyling et al. report less than about 1% of these particles pass to the blood (30). Is this surprising? It is indeed surprising because it has been thought that nano-particles pass easily across the lung to the blood: their small size suggests that this might occur (31). Rather oddly, this assumption is at odds with the theory of filtration of particles: nano-particles are rather well trapped by filters because of their rapid diffusion onto the filter substrate. This, by the way, explains the extensive trapping of nano-particles of less than 10 nm diameter by the nose and pharynx. Whether other nano-particles are also held back, rather effectively, by the air–blood barrier remains to be seen. Geiser et al. have also reported that nano-particles are not very effectively taken up by alveolar macrophages (32, 33). Is this surprising? Perhaps not: macrophages are, so to speak, in the business of clearing bacteria and cellular debris from the alveolar surface; it is at least conceivable that nano-particles are not 'noticed' by macrophages. Of course if nano-particle aggregated in the lining fluid of the alveoli the likelihood of uptake by macrophages would be increased and there is some evidence that this occurs (34, 35). Interaction between nano-particles and the surfactant film that lies on the surface of the alveolar cells has received some attention. Geiser et al. have argued that the surfactant film ensures wetting of the particles and is involved in moving the particles to the aqueous hypophase (36). Damage to the surfactant film, characterised by impairment of the capacity of the film to expand, has also been reported (37). This is clearly, or at least potentially, important: the increase in surface tension of the surfactant film of expansion and its decrease on contraction is essential for alveolar stability. The low surface tension of the surfactant film is also thought to be important for limiting transudation of fluid from the interstitium to the alveolar surface. The limited translocation of nano-particles to the blood is at odds with the well established finding that nano-particles translocate effectively to the interstitium of the lung (38). It has been suggested that some secondary clearance from the interstitium back to the airway surface occurs as part of the process of clearing nano-particles from the lung. The present author and colleagues have recently hypothesised that nano-particles might well penetrate into Type I alveolar cells, induce apoptosis of these cells and then be cleared with the cellular debris by macrophages (39). Whether this will turn out to be true remains to be seen.

Nano-particles and the brain

Nano-particles have been shown to enter the sensory cells of the olfactory epithelium and to be transported via the olfactory nerves to the olfactory lobes of the brain (40). That they enter the nerve a terminal is surprising, that they are transported via the axons to the brain is not. Retrograde axonal transport is a well established process: it explains the movement of the polio virus from skin abrasions to the spinal cord. That nano-particles are transported onwards along the olfactory pathways of the brain is surprising. This implies that they can cross synaptic junctions: how they do this is unknown. It will be appreciated that such findings have the capacity to induce a high level of concern: are the nano-particles of the ambient aerosol, even now, penetrating to our brains?

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Special deliveries and Trojan horses

In discussing the possible effects of nano-particles we should consider how these structures might act. Much depends on whether the material is soluble or insoluble in the tissues. If the nano-particles, or some components of the nano-particles, are soluble then we may be dealing with a delivery-system effect with the transported substance producing its own specific effects. This might well be complicated: nano-particles might reach parts of the body that are inaccessible to the soluble material and thus cause unexpected effects. The possible delivery of metals to the brain is an obvious example, especially if nano-particles can cross the blood brain barrier. That some nano-particles that are used for drug delivery can do this has been established; that engineered nano-particles and ambient nano-particles can do this is less clear. One aspect of what might be called the 'special delivery hypothesis' is the delivery of material to the interior of cells. There is some evidence to show that nano-particles can enter mitochondria: the possibility of activation of apoptotic pathways has been suggested. Xia et al. have examined the effects of ultrafine particles on mitochondrial function (41). In this work diesel ultrafine particles were used and effects on the potential across the mitochondrial membrane were found. This and other effects were attributed to quinones and other organic compounds associated with the particles. But we should ask whether nano-particles locate preferentially to mitochondria in comparison, that is, with location in other organelles and the inter-organelle matrix. This is unknown. Work by Geiser and Kreyling has shown that nano-particles appear to be distributed through the tissues of the lung in accordance with the volume fraction contributed by each type of tissue (42). This suggests a random distribution and not preferential uptake by specific cells. The need to extend this analysis to the distribution within cells is clear. A second feature of the 'special delivery hypothesis' is the potentially high concentration of the leachate (the material that dissolves from the nano-particles) at the site reached by the particles. This might be important, whether it is or not is unknown.

How insoluble nano-particles might damage cells

If we turn to truly insoluble particles then we should consider their effects in terms of their physical presence and, also, in terms of their adsorptive properties. The physical presence of particles within macrophages affects macrophage function. This was shown long ago: rat macrophages can become overloaded with particles and cease to move. Oberdörster has reported that effects on macrophage mobility begin when about 6% of the volume of the cell is occupied by particles. Interestingly, impairment of movement occurs at a lower percentage occupancy (2–3%) when nano-particles are involved (18,43). Why is this? One possible answer is that the key factor that relates to interference with the functioning of intracellular actin is total intracellular particle surface area. Impairment of cell movement and function can lead to necrotic changes in the cell: the process of frustrated phagocytosis seen in macrophages that have bitten off, so to speak, rather more of an asbestos fibre than they can chew, provides an example. That frustrated phagocytosis can occur when macrophages encounter long carbon nano-tubes has been suggested by Poland et al. (23). Adsorption of essential components in the extracellular space might also occur. We have touched on possible effects on surfactant; little seems to be known about adsorption of intracellular substances. Adsorption of extracellular substances might enhance the capacity of nano-particles to cross cell membranes, it is possible that the surface coating might then be removed, perhaps by lysosomes, and the naked nano-particle exposed. If the particle is active in its naked form we might be considering a 'Trojan horse hypothesis'. The key word here is hypothesis.

Human exposures to nano-particles

We are all exposed, continuously, to nano-particles of the ambient aerosol. As one might expect, only a limited number of volunteer studies have been done in this area. Interestingly, Kuschner et al. have reported that exposure to fine and ultrafine magnesium oxide particles produced no signs of pulmonary inflammation as judged by examination of lavage fluid (44). This is a potentially important finding because it casts doubt on the theory that the physical characteristics of the particles control the response and suggests that the chemistry of the particles is important. This study does not seem to have been repeated or followed up.

Hazards and risks

That nano-particle might have toxicological effects is all too clear; what is a great deal less clear is whether they are having such effects now and whether, as a result of exploitation of nano-technologies, they will have effects or increased effects in the future. All toxicologists know the difference between hazard and risk. Discussing these terms again might seem otiose but perhaps this is not so. Consider first the term hazard: the capacity to do harm. Potassium cyanide is undoubtedly a hazard. But what is the risk on exposure to 1ng of potassium cyanide? Most toxicologists would say, none at all. So, if we accept that there is a threshold of effect then at exposures below that threshold potassium cyanide is not a hazard. At exposure above the threshold it is and each exposure is associated with some level of risk: risk being defined as the probability of harm occurring as a result of exposure to the hazard. This is one way of looking at the question;

another is to say that potassium cyanide is always to be defined as a hazard but that at all doses below a certain level the risk associated with the exposure is zero. The standard paradigm of safety assessment of chemicals calls for identification of hazard and then estimation of risk. In the air pollution field this sequence has been reversed: we have discovered the risk associated with exposure to the ambient aerosol and are now struggling to identify and explain the hazard that underlies the risk. As far as we can tell, at a population level, there is no threshold of effect for the effects of the ambient aerosol. The effects with which we are concerned are, in general, not those associated with effects on the genetic material of cells but are effects on the cardiovascular and respiratory systems: effects that are usually thought to be characterised by thresholds of effect. Had any toxicologist been asked, 30 years ago, whether exposure to a few $\mu g/m^3$ of the ambient aerosol would have effects on health he would have replied in the negative. To those working in toxicology and in air pollution science these findings are, or should be, worrying. They show that we cannot predict effects at a population level by toxicological hazard assessment. With the aid of hind-sight this might be explained by arguing that the range of genetic polymorphisms that probably exist within the whole population renders some people more susceptible to the effects of the ambient aerosol than are others. Perhaps so: but what does this tell us about the risks of other materials, nano-materials, to which the whole population might be exposed? It tells me that we should be cautious.

Novel effects and unsupported hypotheses

In studying the toxicological effects of nano-materials we may be faced with a very difficult problem: one is unlikely to see that for which one does not look. Standard toxicological techniques have been developed to look for the effects of chemicals and the effects that are looked for are those that are well described and, to some extent, understood. How then should we react to the suggestion that nano-materials might have unexpected toxicological effects? Let us imagine that it were to be suggested that exposure to nano-particles increased, to a modest extent, the likelihood of development of Alzheimer's disease. Would we be able to predict this by means of a standard toxicological screening battery? Do rats or other commonly used laboratory species develop Alzheimer's disease? One would be unsurprised if the answers to both questions were, no. A neuro-toxicologist would perhaps argue that methods that do allow subtle effects on the central nervous system to be detected have been developed. No doubt this may be so but including them in a standard test battery would be costly. The parallel with the air pollution field is clear: it would not have been predicted that exposure to the ambient aerosol causes accelerated thickening of the walls of the carotid arteries of people. But we know that this occurs from epidemiological studies in man (45). Standard screening batteries do not look at arterial wall thickness; of course if the changes were gross they might be noticed on histological examination of tissue removed post-mortem, but modest effects might well escape attention. This gets to the heart of toxicology: if you give big doses to experimental animals and don't see effects, people should be safe, even allowing for interspecies and intra-species differences in sensitivity, at much lower levels of exposure. But this assumes you know what you are looking for: some would say that this was an unwise assumption in the context of nano-toxicology. The danger here is that effects that would go undetected in standard toxicological product-screening can always be suggested. Whether these effects are possible, let alone likely, is another question. Let us imagine, for example, that I suggest that nano-particles can enter the dendritic cells (cells that are key to antigen presentation to lymphocytes) of the walls of the airways. This is, in fact, not unlikely: these cells take up antigen. Let me also suggest that the uptake of nano-particles impairs the functioning of these cells. I have no idea whether this is true: I have certainly never heard it suggested. Would malfunctioning, perhaps rather minor malfunctioning, of these cells be detected by standard toxicological methods? Indeed not. Would malfunctioning of these cells affect the capacity of some people to resist respiratory infections? It might. The danger is clear: if the utterly unsupported, but not entirely implausible, hypothesis is accepted then the deduction is not at all unreasonable. That suggestions such as this will be made as nano-technology expands and people are, perhaps, exposed to a greater variety of nano-particles, is certain. Deciding how to respond to such suggestions is part of the challenge of nano-toxicology.

Exposure

We have considered hazard and risk and it seems certain that some nano-particles constitute a hazard and, if exposure occurs, might pose a risk to health. If? Yes, if exposure occurs. How likely is exposure to nano-particles? Exposure to the nano-particles of the ambient aerosol is certain as long as people need to breathe. Exposure to nano-materials developed for use in medical diagnostic methods and in therapy will be limited to those requiring such assistance. We might expect that Regulatory Authorities concerned with the safety of drugs and medical appliances will insist on rigorous testing of these products. In addition, any risk to patients should be balanced against the benefits conferred by better diagnosis and therapy. More worrying are engineered nano-particles which might be incorporated into a wide range of products and encountered, essentially unwittingly, by the public. Whether exposure to the nano-materials

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incorporated into products for general use is likely is a moot point. The tennis player grasping the handle of a racket with a form of nano-carbon fibre bonded into its structure is in contact with a nano-material bound into a matrix. That he will inhale nano-fibres released from his racket is very unlikely. But the person wearing odour-eating socks might be in rather closer contact with nano-particles of silver attached to the fibres of the sock. Will these particles be absorbed via the skin? Will these particles be released into the effluent from his washing machine when he washes his socks? And, if so, will the silver particles endanger invertebrates in the water course to which the effluent runs? These questions remain to be answered.

Exposure to nano-particles used in commercial products might occur at three main stages of the product cycle. The first is in construction of the product: occupational exposure of the workers making the product. This is possible, indeed likely, unless precautions are taken. Exposure could occur during the production of the nano-material or during its incorporation into final products. The problem here is one of occupational hygiene and advice has been provided on this in the UK by the Health and Safety Executive (46). Exposure during product use is less likely but exposure as a result of product disposal is possible and is a cause of some concern. Materials containing nano-materials may be disposed of to land-fill and as the products breakdown nano-materials may be released to water courses. Burning may also release nano-materials. Concerns about the possible asbestos-like properties of nano-tubes have led to advice that these materials should be treated as if they were asbestos. This will impose strict requirements on those dealing with the disposal of such materials.

Conclusions

Nano-technology is new and is expanding rapidly. As with perhaps all new technologies benefits will be conferred and risks will be encountered. Identifying the risks to health before damage to health occurs is the task of the nano-toxicologist. This is by no means an easy task: as yet we are unlikely to know about all the risks for which we should be looking. Research is needed. Industry might reasonably be required to take charge of investigating the safety (or danger) of their products but an extensive programme of basic research is needed to identify possible risks and to work out the mechanisms by which nano-materials might affect the body. Such research requires funding from government: it is encouraging to know that in the UK such funding is being provided and that a National Nano-toxicology Research Centre has been established by the Health Protection Agency. Will this be enough? I suspect not. Nano-technology runs the risk of becoming a perfect 'scare story' for the media and public confidence could easily be lost. One has only to look at the furore over GM crops to see what might happen.

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