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Phil. Trans. R. Soc. Lond. A 2000 **358**, 2673-2682
doi: 10.1098/rsta.2000.0676

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Inhaled ultrafine particles are increasingly being recognized as a potential threat to health. Aerosols in workplace environments may come from a wide variety of sources, depending on the type of activity and processes taking place. Some activities and processes are acknowledged as being 'dusty', where aerosol is generated from the mechanical handling and attrition of solid or liquid material, and are not considered to be plausible sources of ultrafine particles. However, hot processes, involving the vaporization of material, and inevitable subsequent cooling, do have the potential to generate significant number concentrations of ultrafine particles. However, consideration of the physical conditions required for the generation of particles in the range below 100 nm suggests that those conditions are not easily met in workplaces. More generally, the conditions are such that particles grow out of this range, either by continuing condensation (as happens at high vapour concentrations) or by agglomeration between smaller particles (as happens at high number concentrations). Not much is known about ultrafine particles in actual workplaces, mainly because our view has been obscured for the past few decades by the fact that most occupational aerosol standards have been based on the mass concentration of airborne particulate matter. Now that a new awareness has set in, it is expected that new research will address the problem.

Most current aerosol standards are expressed in terms of the mass concentration of particulate matter conforming to a particle size fraction, where the latter is based on knowledge of how particle size relates to where particles deposit in the human respiratory tract and any subsequent effects. At present no such basis exists for ultrafine particles, but one is needed before progress can be achieved towards meaningful standards for occupational ultrafine aerosols. It is expected that, for ultrafine particles, such a standard may, in the future, be expressed in terms of the number concentration of particles less than a certain size, that size to be determined on the basis of the physical and chemical nature of the particle at that size, human physiology and toxicology.

Keywords: workplace; occupational exposure limits; ultrafine particles; occupational hygiene; nucleation; particle-size-selective criteria

1. Introduction

There was a time when, to occupational hygienists and physicians, 'fine' particles were considered to be those which, after inhalation, could penetrate down to the alveolar region of the lung—what is now referred to as *respirable aerosol*. More recently,

Phil. Trans. R. Soc. Lond. A (2000) **358**, 2673–2682

interest has been drawn towards still finer particle fractions, not least because of their possible association with health effects specific to those sizes of particle. The term *ultrafine* is used broadly to refer to particles whose diameters are less than 100 nm (0.1 μm), and the use of that term seems to suggest that such particles represent the ultimate in 'smallness'. However, that definition, appearing to reflect a boundary that defines what is less harmful (above) and what is more harmful (below), is somewhat arbitrary and needs to be carefully examined.

Interest in still smaller particles in the range a long way below 100 nm is stimulated in large measure by some of the technology-oriented aerosol research which is beginning to yield insights into the physical nature of such particles and their reactivity and how such knowledge can lead to exciting new engineering applications (Pui *et al*. 1998). But there is growing awareness that the very same properties that lie behind such interest might also have a significant bearing on the possible health effects that might arise when ultrafine particles are inhaled by humans and come into contact with living tissue. All discussion about the reactivity of ultrafine particles in such scenarios must begin with the physical nature of the particles themselves. In his review, Preining (1998) described how, as particles become smaller and smaller, their physical state becomes distinctly different from that of larger particles from ultrafine upwards, where the number of molecules or atoms the particle contains becomes so few that a high proportion of them lies at the surface of the particle. For example, a 20 nm particle has 12% of its molecules at the surface. This fraction rises to 25% for a 10 nm particle. Here, therefore, even the concept of a 'surface' has limited meaning because the material structure of the particle can no longer be regarded as a continuum. Thus, according to Professor Preining, the material itself can no longer be thought of simply as 'solid' or 'liquid', and we enter the world of 'cluster physics', where such considerations may become very important in relation to how such particles interact with other molecules and particles. In turn this provides much food for thought in relation to how such particles might interact with biological organisms or cells, and, hence, on their potential toxicological effects.

2. Ultrafine particles in living and working environments

Much of the current interest in ultrafine particles has stemmed from growing concerns about the role of such fine aerosols in the observed increases in deaths from cardiovascular and respiratory causes (Seaton 1996). Although the net amount of urban particulate air pollution, as expressed in terms of airborne mass concentration, has decreased with reductions in particulate emissions from industry and power stations under clean air regulations that have been enacted in many countries, it is recognized that the nature of urban atmospheric aerosol is now distinctly different. Now, although mass concentrations have fallen, the number concentrations of very small particles, associated for example with emissions from internal combustion engines, has increased. For example, Kittelson (1998) has noted that, although the latest generations of diesel and spark engines are improved in terms of the mass of particulate emissions, the *number* of nano-sized particles emitted has increased sharply. This may also be true for emissions from aircraft engines.

So this changing nature of urban atmospheric aerosol, coupled with the public health epidemiology, is driving much of the discussion on health effects associated with atmospheric aerosol fractions finer than the ones that have been considered in the past. It is also stimulating discussion about workplace aerosols, and an examination of the extent to which occupational health might be similarly impacted by workers' exposures to very small particles. Here it is important to note, firstly, that the occupational environment in general represents a major consideration in public health, since a very high proportion of the population goes to work and, in the process, may be exposed, largely involuntarily, to occupation-related hazards. It was recognized very early on in the 1900s that aerosols in workplace atmospheres contributed to major disease epidemics affecting whole communities (e.g. mining, agriculture, etc.), and so aerosol science became a very important part of the growing field of occupational hygiene science (Walton & Vincent 1998).

Workplace aerosols of interest to occupational hygienists are those that are released into the working environment. Depending on local factors such as workplace layout, the processes going on there and the ventilation, the aerosols to which workers are exposed are likely to be very 'fresh', usually no more than a few minutes old. The range of aerosol types (i.e. chemical composition) and particle sizes can range very widely, and may be roughly categorized as follows.

(i) Dust and sprays from mechanical processes (e.g. mining, textiles, chemical manufacture and transportation, agriculture, etc.), with particle sizes mainly greater than 1 μm ranging all the way up to 100 μm and (even) beyond.

(ii) Fumes from hot processes (e.g. smelting and refining of metals, welding, etc.), with particle sizes usually not much greater than about 1 μm and going down to a few nanometres (i.e. the size of primary particles produced by nucleation).

(iii) Fumes from combustion processes (e.g. transportation, carbon black manufacture, etc.), usually associated with incomplete combustion, again with particle sizes not much greater than about 1 μm but going down to a few nanometres.

(iv) Bioaerosols (e.g. agriculture, biotechnology, etc.), where some particles (e.g. viruses, endotoxins, etc.) may be as small as a few tens of nanometres.

Ultrafine aerosols arising from mechanical processes (e.g. the breaking or fracture of solid or liquid material) are generally unlikely. One possible exception is in the production of very small solid particles from sprays of dilute aqueous solutions like those found in some humidification systems (Vincent 1970). Greater potential for ultrafine particle production exists where there are hot processes or combustion, and where very small particles may be created by the physical process of nucleation from the vapour phase. Such nucleation may take the form of homogeneous nucleation and condensation, by which particles are formed initially by the spontaneous condensation of molecules from the gas to the liquid phase; or heterogeneous nucleation, by which particles are formed by the condensation of molecules onto pre-existing very small nuclei.

3. Ultrafine particles in occupational hygiene

The discipline of 'occupational hygiene' is defined as the anticipation, recognition, evaluation and control of workplace hazards. Yet ultrafine particles have received little attention, either by scholars or practitioners in the field. This lack can be understood from the history of how criteria have evolved for occupational aerosol exposure assessment and standards (Walton & Vincent 1998). In the early 1900s, when it became widely recognized that workplace aerosols were potentially injurious to health, airborne particulate matter was assessed by collecting samples in very rudimentary sampling systems (e.g. with cotton wool filters) and weighing what was collected, from which estimates of mass concentration of the aerosol in question could be made. At that time, therefore, exposure was thought of in terms of particulate mass concentration, and environments were regulated and controlled on that basis. By the 1920s, however, it became recognized that particles below a certain size were the ones primarily associated with mining-related lung disease (e.g. pneumoconiosis) (McCrea 1913). So for many years it was customary in the countries then prominent in occupational hygiene (e.g. the UK, USA, South Africa, Canada, Australia, etc.) to assess occupational aerosol exposures in terms of the number concentrations of particles with diameter less than 5 μm, as evaluated by optical microscopy. Standards for occupational aerosol exposures were correspondingly expressed in this way. It was only in the 1950s that this convention was revisited, leading to the concept that sampling of such aerosols should be carried out in a way that reflects how inhaled particles are aerodynamically transported inside the human respiratory tract and deposited in the various regions of the lung. This led in turn to the development of particle size-selective sampling devices that reflected much more closely the true nature of human exposure and could provide mass concentrations of aerosol in an appropriate particle size range. Epidemiological studies subsequently showed that exposure, expressed in terms of the mass concentration in health-relevant particle size fractions, correlated much better with the prevalence of many lung diseases than the previous index based on particle number concentration. It has remained that way to this day, although the system of conventions for particle size-selective sampling and standards has more recently been expanded (see below). So almost all occupational exposure limits (OELs) for aerosols, with the exception of asbestos and radioactive aerosols, are expressed in terms of mass concentration.

The effect of this history, especially over the past 40 years, has been to focus attention with respect to occupational aerosols on mass concentration as the primary, and most relevant, index of exposure. For ultrafine particles, even though in many instances they might represent the vast majority of the number concentrations of particles in many workplace aerosols, they nearly always represent an infinitesimal proportion of the mass concentration. As a result, ultrafine particles have never appeared in our consciousness. In turn, there is very little to report on how they appear in the overall characterization of workplace aerosols. There are just a few exceptions.

There has long been concern about diesel particulate arising from the use of diesel-powered vehicles in confined industrial spaces (e.g. mines). Here, the numbers of exposed workers around the world are very large. Knight *et al.* (1983), and others since, have examined the particle size distribution of the aerosol in such environments, and have shown significant number concentrations of particles in the range below 100 nm. More recently, Professor Kulmala and his co-workers in Finland (Hämeri *et al.* 1996) reported a study of aerosol generation during the process of ski hot-waxing using fluor powder, where (perhaps surprisingly) over 10 000 people are exposed in Finland alone. They demonstrated that, at certain stages of the hot-waxing process, significant number concentrations of particles are created by nucleation and may occur in the particle size range below 100 nm.

The question of ultrafine particles has been raised in relation to occupational metals exposure, although the available information is somewhat anecdotal. Sandström *et al.* (1989) described incidents that happened in rapid succession early in 1943 at a Swedish smelter, where 13 workers were taken ill. One died of acute respiratory distress syndrome (ARDS), supposedly after exposure to fine particulate nickel; two others died of ARDS supposedly after exposure to fine zinc chloride smoke. The most well-documented, and somewhat similar, case was reported by Rendall *et al.* (1994), describing an occurrence at a South African plant where the arc spraying of nickel was being used to coat metal components. In the process, an arc was created between two nickel wires which were being fed continuously into the jet of a compressed air-driven spray gun. The fine nickel particles were carried away very rapidly by the air jet from the immediate region of the arc and then deposited on the component in question. The first time that the process was used, the operator was soon taken ill, and died a few days later of ARDS. Urine samples, taken before he died, showed a nickel concentration of about 700 $\mu g\,l^{-1}$, a level which was regarded as 'excessively' high. Following the death of the worker, an investigation was carried out that included a simulation of the process he was operating when he became ill (although, of course, the operators this time wore rigorous personal protective equipment). Electron microscope analysis of aerosol samples revealed very large number populations of nickel particles with diameter less than 50 nm.

4. The physical scenario

In reality, quite stringent physical conditions need to be met if truly 'ultrafine' particles are to be generated, most notably to ensure that

(a) the primary particles formed by nucleation do not grow to sizes outside the ultrafine range, and

(b) the primary particles undergo minimum coagulation.

The conditions 'favourable' for the generation of ultrafine particles may be summarized as follows:

(i) there must be vaporizable material present;

(ii) the temperature or heat transfer should be sufficient to produce just enough vapour to condense as an independent aerosol, but producing a low number concentration of primary particles;

(iii) there should be rapid cooling of the aerosol that has been formed and a large temperature gradient.

The first of these is obvious. But the other two are more subtle. Below a certain amount of vaporization (as reflected in vapour concentration), the vapour that is present will not nucleate and condense independently, but, rather, will condense on pre-existing and (usually) non-ultrafine particles. This is the case, for example, with involatile radon daughters following the radioactive decay of radon gas. It has recently been found that a condition for the nucleation of initially ultrafine aerosol in Finnish forests is that the concentration of condensing vapour is high enough (Clement *et al.* 2000). This concentration is given by its production rate from solar radiation divided by the removal rate onto existing aerosol. So the observation establishes the need to produce a large enough vapour concentration in the atmosphere, especially when existing aerosol is present. The low concentration requirement ensures that subsequent particle growth by coagulation is minimized. For the third condition, the rapid cooling greatly enhances the probability of nucleation and independent particle production, ensuring that the aerosol is 'frozen' and does not continue to evolve such that the particles continue to increase in size by ongoing condensation.

A typical example where such conditions might be met in an industrial setting might be the heating of a small amount of material by, say, a laser spot. The temperature is very high, but only a very small amount of material is available to be vaporized. So the capacity for growth of the original nucleated particles is limited. Also the number concentration of the newly formed particles is similarly limited at the outset. Further, the very sharp temperature gradient allows the aerosol to be 'frozen' early on in its evolution. With this in mind, therefore, localized heating of volatile material by lasers or arcs might be seen as highly conducive to the production of ultrafine particles, and, hence, might be seen to be potentially the most dangerous. Although the events and subsequent investigation reported by Rendall *et al*. (1994) represent what appears to be an isolated case, and are not documented in a way that allows close inspection in relation to what is currently known about the potential for the generation of ultrafine particles and how they might lead to ill health, it is interesting to note that the scenario is strikingly similar to that described here as being 'favourable' for ultrafine aerosol production.

In general, however, it might be said that the stringent conditions for ultrafine particle formation might be difficult to meet in most of the workplace situations characterized by hot processes. Such conditions are not satisfied, for example, in large-scale accident scenarios associated with overheating in the nuclear industry, where typical particle sizes are of the order of 1 μm or larger (Schikarksi 1988). It is also likely that they will not be met in most large-scale metals smelting and refining processes, one area where concern about ultrafine particles has already been expressed.

5. Health-related standards for aerosols

An ideal standard for any airborne contaminant should include (Vincent 1995):

(i) criteria for exposure, which identify the agent and its specific physical, chemical and/or biological properties relevant to a specific adverse health outcome;

(ii) reference to monitoring instruments and analytical methods with performance characteristics matching the defined exposure criteria;

(iii) reference to a monitoring strategy which sets out to assess exposure in a manner which is representative of the temporal histories and variability of workers' exposures; and

(iv) a health-based OEL derived from considerations of the effects of exposure at various levels, known incidences of the prevalence of the health outcome in question, and what might be an 'acceptable' level of risk.

When the standard is set out in this way, it becomes obvious that, strictly, an OEL cannot be assigned until consideration has been given to the other items listed. This is particularly clear for aerosol exposures, where the evaluation of the health effect includes not only consideration of the intrinsic toxic properties of the particulate material in question but also its physical properties (i.e. particle size, shape, density), which govern how the particles are transported within the respiratory tract and their subsequent fate after deposition. For such exposures, research has delivered a good understanding of the physical nature of how airborne particles are inhaled and, based on knowledge of nasopharynx and lung physiology, how they penetrate to and are deposited in the various parts of the respiratory tract.

From such understanding, particle size-selective criteria have been proposed, identifying:

(i) inhalable aerosol, the fraction of particles that may be inhaled through the nose and mouth during breathing;

(i) thoracic aerosol, the fraction that may penetrate beyond the larynx and so enter the lung; and

(i) respirable aerosol, the fraction that may penetrate beyond the airways of the lung and enter the gas-exchange region.

Each of these fractions is described as a curve that expresses the probability of entry or penetration as a function of particle aerodynamic diameter (which mainly governs the physics of particle motion that influences these fractions). In turn, such curves become the yardsticks against which to relate the performances of sampling instruments that will provide scientifically defensible measures of exposure in a way that relates directly to the health effect of interest. For example, respirable aerosol would be chosen as the metric most appropriate to pneumoconiosis, a disease of the gas-exchange region of the lung; while inhalable aerosol would be chosen as the metric most relevant to health effects associated with airborne lead, since all the lead that is inhaled may contribute to lead-related ill health. In turn, therefore, such fractions become sensible bases of standards. Indeed, they underpin the new generation of occupational aerosol standards that is emerging, and on which—over the 20 or so years of their development—a considerable degree of international harmony has been achieved, involving the International Standards Organization (1992), the Comité Européen de Normalization (1992) and the American Conference of Governmental Industrial Hygienists (2000, see also editions from 1993 onwards). Furthermore, of these, the ISO standard is aimed also at aerosol exposures in the ambient atmosphere, and so goes beyond just workplaces.

For ultrafine particles, no such criterion has yet been established upon which to base a standard for the protection of workers. Although 'less than 100 nm' has been identified as a working definition of what is currently referred to as an 'ultrafine' particle, there is at present no physiological or toxicological basis by which to establish a criterion for exposure assessment that, in turn, following the framework outlined above, can form the basis of a scientific standard. Some basic biological research has been conducted to ascertain the specific characteristics of very fine particles, in the size range from about 10 nm (0.01 μm) up to about 500 nm (0.5 μm), in relation to what makes very fine particles more toxic to biological systems than larger particles of the same material (see, for example, Oberdörster *et al*. 1992, 1995; Donaldson *et al.* 1998). The results suggest that the ultrafine particles are much more toxic, although their interpretation is complicated by the fact that, for given particulate mass, particle numbers and particulate surface area increase sharply in this range.

Seaton and co-workers (Seaton *et al.* 1995; Seaton 1996) have considered the possible causative factors linking exposure and the observed mortality in the general population. They proposed a hypothesis in which exposure to ultrafine particles in the size range around 50 nm:

> . . . characteristic of air pollution (may) provoke alveolar inflammation leading to acute changes in blood coaguability . . . [and] result in an increase in the exposed population's susceptibility to acute episodes of cardiovascular disease; the most susceptible suffer the most. This hypothesis, being based on the number, composition and size—rather than on the mass—of particles accounts for the observed epidemiological relations.

However, that there is at present no specific health-related particle size-selective criterion for ultrafine particles reflects the fact that there is insufficient knowledge about cause and effect to permit such a criterion. But, because of the interest stimulated by concerns about health effects in populations exposed to such fine aerosols in workplaces, as well as in the ambient atmospheric environment, it is likely that new research in the years ahead will address the problem. Nevertheless, we may for the time being speculate that a future standard for very, very small particles will be expressed in terms of the concentration of particles less than a certain diameter *according to some metric other than mass* (e.g. number or surface area concentration). That diameter may be in the range of a few nanometres up to a few tens of nanometres, and will be based on new knowledge about the nature of such small particles such that they produce a different—and enhanced—response in exposed people. The concentration that will become the OEL will be determined on the basis of the physical and chemical nature of the particle at that size, human physiology and toxicology. When that criterion eventually emerges, appropriate instrumentation for occupational exposure assessment will be needed. Fortunately, in this regard, aerosol scientists and engineers have already developed a range of sampling and analytical principles and devices that can be used for this purpose (Pui 1996).

6. Conclusions

Ultrafine particles are increasingly being recognized as a potential threat to health. Aerosols in workplace environments may come from a wide variety of sources, depending on the type of activity and processes taking place. Some activities and processes are acknowledged as being 'dusty', where aerosol is generated from the mechanical handling and attrition of solid or liquid material, and are not considered to be plausible sources of ultrafine particles. But hot processes, involving the vaporization of material, and inevitable subsequent cooling, do have the potential to generate significant number concentrations of ultrafine particles. However, consideration of the conditions required for the generation of large concentrations of particles small enough to be regarded as 'ultrafine' suggests that those conditions are not easily met in workplaces. However, very little 'hard' information is available about ultrafine particles in workplaces, mainly because our search for knowledge has been obscured for the past few decades by the focusing of most occupational aerosol standards on the mass concentration of airborne particulate matter. This is clearly an area where further occupational hygiene research is called for.

As mentioned, most current aerosol standards are expressed in terms of the mass concentration of particulate matter conforming to a particle size fraction, where the latter is based on knowledge of how particle size relates to where particles deposit in the human respiratory tract and any subsequent effects. At present, no such basis exists for ultrafine particles, but is needed before progress can be achieved towards meaningful standards.

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Discussion

R. Agius (*University of Edinburgh, UK*). I have a comment regarding nickel toxicity. In the case reported by Rendall *et al.* (1994), the presence of nickel in the urine provides only limited evidence of the time-scale and 'species' of the exposure. Biological monitoring studies have shown that at an individual level the short-term correlation between urinary levels of nickel and exposure is poor, and inhalation of a number of species of nickel or its compounds (as occurs, for example, in welding) can be responsible for elevated urinary nickel. The Australian aqueous refining process which has been remarked upon as a possible source of occupational exposure to particulate elemental nickel is unlikely to have generated ultrafine particulate from an aqueous precipitate. Theoretically, in nickel refining, the likeliest exposure to ultrafine nickel would have arisen in the Mond process after decomposition of nickel tetracarbonyl. This process has resulted in many fatalities. However, the intrinsic toxicity of the tetracarbonyl renders it almost impossible to determine whether or not the ultrafine elemental nickel per se contributed to the toxicity.