Aerosol exposure: concepts, criteria, standards and applications

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Abstract. This paper places Inhaled Particles X in the context of the whole sequence of such symposia, going back to the first one in 1961. It draws together some of the essential principles that have been learned since that earlier meeting about the nature of exposure and exposure assessment and thus provides a framework by which to integrate the new knowledge presented at this latest one. In the process, the importance of understanding the formal definition of aerosol exposure is stressed, including the distinction between exposure intensity and exposure history, and how that relates to some measure of cumulative dose which, in turn, may be linked with knowledge about intrinsic toxicity, etc. This then leads to a definition of exposure standards, and the important ingredients of criteria, sampling and limit values. A summary is provided of the current set of particle size-selective criteria that have been widely agreed in the international occupational and environmental health community. Some ideas are presented about how this set might be expanded for certain applications, the important case of ultrafine aerosols being one of them.

1. Introduction
The first BOHS-sponsored "Symposium on the physical, chemical and physiological factors governing the entry of harmful substances into the body via the respiratory system" took place in Oxford in March 1961, and the proceedings – Inhaled Particles and Vapours – appeared the next year, edited by C. Norman Davies, one of the pioneers of what we now know as ‘aerosol science’. Over the years since, a succession of nine such symposia has appeared, each reflecting the latest (and best) work in what has continued to emerge as a field important to occupational and environmental health (and to public health more generally). In the 1997 proceedings of the eighth symposium in the series, W. Henry Walton – who himself was editor of many of the later volumes – published a short history of what had been achieved over the preceding years, noting that the original statement of intent made no mention of clearance, biological responses or epidemiology arising from aerosol exposures, but that these became important components of the later meetings.[1]
Now, at the Tenth Inhaled Particles Symposium (IPX), marking an important milestone in this unique series, it is appropriate to re-visit the original aims, and to relate them to how the symposia has evolved and expanded over the years. As a starting point, Figure 1 draws together schematically the various environmental health considerations as they apply to aerosols, and argues that exposure is the central issue. The aerosol hazard may be present in the environment, but exposure occurs only when people interact with that environment. Once exposure occurs, however, it may be followed by a succession of pharmacokinetic and toxicologic processes inside the exposed organism that may or may not lead to an adverse outcome in the form of a clinically or pathologically identifiable disease. The relationship between the exposure and some such outcome may be studied by enquiring into the qualitative and quantitative nature of those intermediate processes, by what we may term as the ‘risk sciences’. Or it may be studied by exploring the quantitative associations by means of the tools of epidemiology. Or by some combination of the two. Here, it should be noted that difficult questions about the detailed roles of toxicity and biochemistry are particularly important – indeed crucial – for exposures where the aerosols comprise complex mixtures, even more so for environmental than for most occupational exposures.

Once the exposure-outcome relationship is determined, by whatever means, there emerges a basis for setting a meaningful standard. The purpose of the standard then becomes the instrument by which to determine the extent to which people may be at risk and to indicate where remedial measures are needed. For the latter there are options for technical control directly of the hazard itself (e.g., by elimination), or of the environment (e.g., by ventilation), or of the way in which people interact with their environment (e.g., by job rotation, or respiratory protection). Beyond these options, there may be some situations (e.g., exposure to certain biological organisms) where there might also be the possibility of intervention in the biological processes inside the exposed individual (e.g., by immunization). The picture described in Figure 1, or something like it, becomes a comprehensive
framework by which we may think of the problem, putting it all together, and identifying the diverse roles of the participating individuals and their respective disciplines.

2. Background
For aerosol exposures, the question of the nature of exposure was addressed closely by the occupational health community in the years leading up to the first Symposium. It had long been recognized that certain types of disease among mineworkers were strongly associated with the exposures to airborne dust. In the early 1900s clear evidence emerged from examination of lung tissue from miners recovered at autopsy that pneumoconiosis was a disease of the alveolar region of the lung; and further that only a fine particle fraction of inhaled aerosol was able to penetrate so deeply into the respiratory tract.[2] This knowledge provided the basis of the first criteria for aerosol exposure assessment in which only the fine particles considered to be relevant to the disease were to be included. Not long afterwards, a number of novel particle size-selective sampling instruments appeared. A famous example was the kometometer, widely used in the mining industries in several countries, in which sampled aerosol was deposited by impaction onto a glass slide and particles with width (when viewed under an optical microscope) less than 10 μm were subsequently viewed by microscope, sized and counted.[3] Much later, during the 1950s, the role of aerosol physics in the penetration of particles into – and regional deposition in – the human respiratory tract began to be clarified by the efforts of some of the leading aerosol scientists that had been drawn into this field, including most notably the aforementioned Norman Davies and Henry Walton. Their insights led to the definition of the respirable fraction by the British Medical Research Council.[4] Based on the earliest experimental inhalation studies with human volunteer subjects, the respirable fraction set off in the first instance to reflect the aerodynamic particle size dependent-penetration of particles down to the alveolar region. The convention that was ultimately adopted was chosen on the basis of how such penetration might be mimicked in a sampling instrument, specifically the horizontal elutriator.[5] In making this choice, it was tacitly assumed that the proportion of inhaled fine particles that remained airborne for long enough to be exhaled could be neglected. The convention took the form of a curve describing the probability of penetration as a function of particle aerodynamic diameter \(d_{ae}\) - defined as diameter of an equivalent spherical particle of density \(10^3\) kg/m\(^3\) having the same falling speed in air as the particle in question - and immediately became known as the ‘BMRC curve’. This was later recognized by the wider occupational health community during the Johannesburg Pneumoconiosis Conference in 1959, and subsequently became known to many as the ‘Johannesburg curve’. Soon afterwards, other versions of the respirable fraction were proposed, including one by the American Conference of Governmental Industrial Hygienists (ACGIH) that was capable of being followed by a small personal sampler based on a miniature cyclone.[7]

3. Exposure concepts
The thinking behind these early definitions of a fine aerosol subfraction of what is inhaled provides a basis for a general definition of aerosol exposure. One version is that exposure may be defined as the intensity of the agent of interest at the relevant interface between the environment and the biological system representing the exposed subject. Here, therefore, in relation to the preceding, the relevant interface is the alveolar surface of the deep lung, and the intensity is the aerosol concentration there reflecting the flux of particulate material that may pass to the subject. This definition, however pedantic, is useful because it can be generalized to other aerosol fractions (e.g., that deposited in the airway region). Indeed, it may also be applied in environmental health more widely to other potentially harmful agents.
Some qualifications are required. Exposure intensity is a scalar quantity that takes instantaneous values. Or it may be averaged over time, which may be short (e.g., from a few minutes up to many hours, a working shift perhaps) or long (e.g., a subject's lifetime). A hypothetical yet typical aerosol exposure scenario of an individual worker is given in Figure 2. Figure 2a illustrates how the exposure might vary during a single working day, including a period of low exposure during the individual's lunch break. The continuously-varying line indicates the changing instantaneous levels of exposure, and the flat, straight line represents the corresponding 8-hour time-weighted average (TWA). Figure 2b extends this idea to a much longer period, which might be as long as the individual's working life. Now the continuous line represents the changing 8-hour TWA levels, and the shaded boxes represent averages over much longer intervals that might represent the results of periodic sampling campaigns (e.g., as obtained during the large, long-running project conducted in the British coal mining industry known as the Pneumoconiosis Field Research, [8]). In both the short and the long terms, it is well known that exposure is highly variable, driven by factors relating to both the nature of the hazard (and how it is generated), the environment itself, and the individual human subject. In addition, Figure 2b shows hypothetically how, over the years, the exposure levels may fall steadily as standards become stricter and more stringent controls are implemented. Figure 2b may therefore be regarded as the worker's exposure history.

Exposure history is one ingredient in the risk science that is applied within the framework outlined in Figure 1. Another is the dose of the particulate material at relevant sites in the respiratory tract and beyond, reflecting how much is deposited and where, and its subsequent fate. How much is cleared, and how fast? How much remains, or is transferred to other tissue? Some of the physiological mechanisms governing dose are quite fast, with time constants of the order of hours or days, others quite slow, of the order of months and years. Then there is the toxicity of the material, referring to its...
action at given locations and biological responses that are induced, along with the biochemistry that
governs changes in chemical form or persistence of the material in its ability to be harmful. All these
remain outside the scope of this paper, but are the subjects of many contributions elsewhere at this
Symposium. Suffice to say for the present that all events and processes leading to adverse health
outcomes are driven in the first instance by the exposure.

A significant point within this discussion is contained in the question: to what extent might the
influence of recent exposures influence the adverse outcome in relation to exposures that happened in
the distant past? It is unlikely that their impact will be the same. With this in mind it might be argued
that, in occupational epidemiology, the invocation of a cumulative exposure obtained by simply
adding together all the exposures over the lifetime of the exposed individual is not quite ideal. In
fairness, many epidemiologists have recognized this notion and the weakness it brings to their
analyses, and – indeed – some have attempted to account for it by introducing concepts such as lag
time.[9]

4. Exposure standards

Occupational and environmental exposure standards may take two forms: (a) regulatory standards,
applied and enforced by national governments, built within overarching occupational health policies;
and (b) guidance standards, usually offered by private organizations (e.g., ACGIH for occupational
exposures) aimed at providing benchmarks to guide the efforts of health professionals.

An occupational or environmental health policy may be described as the outcome of discussion
between individuals (or groups of individuals), often representing parties with competing interests,
who strive to influence an end point which takes the form of occupational health-related legislation
and regulation. The content of such discussion is usually based on existing public health data records
describing the incidence of disease and its associations with environmental factors. The end point is
usually based on some sort of consensus about the ways in which occupational health is valued in a
responsible society, and about what is and what is not acceptable. A standard for a given agent derives
from the specific value that society gives to a particular aspect of adverse health outcome, and to the
factors which influence it or are influenced by it. If the policy justifies and defines the problem and
provides a regulatory framework for addressing it, incorporating all diverse factors which society at
large needs to take into account, a standard provides a measurable reference point consisting of
specific guidelines by which the desired objective can be quantified and achieved.

As long ago as 1993,[10] this author defined an exposure standard in terms of a set of ingredients:
(a) a set of one or more criteria providing a scientific basis by which to define quite specifically the
agent of interest, including which chemical species and – for aerosols – which particle size fraction is
the most appropriate to the health effect in question; (b) measurement instrumentation, accompanied
by appropriate sampling strategies and analytical procedures, that allow quantitation of the agent of
interest in a way matching the criteria defined at the outset; and finally (c) a limit value that provides a
quantitative yardstick for what is, and what is not, permissible exposure. Specification of the limit
value must match the initial criteria and must relate to the identified measurement methods. So (c)
cannot be assigned without prior reference to (a) and (b).

5. Exposure criteria for aerosols

Much of the discussion about exposure criteria for aerosols relates to the physical properties of the
particles governing how much is deposited in the human respiratory tract, and where. It is well known
that the entry of particles into the body through the nose and mouth during inspiration, and deposition
at defined regions within the respiratory tract, and governed by physical processes, including for the
larger particles (generally larger than 1 μm in diameter) the aerodynamics of inertial movement and
gravitational settling, and for smaller particles (generally smaller than 1 μm) the thermodynamics of
diffusion. The early recognition of the role of finer particles in the dose of particulate material to the
alveolar region of the lung has already been described. Over the years since those pioneering efforts, a more comprehensive set of particle size-selective criteria has emerged, based on the large amount of experimental data from wind tunnel experiments with inert-but-breathing mannequins and studies of particle inhalation under highly-controlled conditions using human volunteer subjects. Now there is wide international acceptance of a framework that includes, for occupational exposures, the *inhalable fraction* (the particle size-dependent fraction of particles that enter through the nose and/or mouth during breathing), the *thoracic fraction* (the fraction of particles that penetrate below the larynx and into the lung) and – again – the *respirable fraction* (the fraction of particles that penetrate down to the alveolar region). The latter part is consistent with the earlier definitions of the respirable fraction, but the detailed form of the definition has been updated in the light of later information. The set of criteria that has gained widespread acceptance is the harmonized version promulgated by the Comité Européen Normalisation (CEN), the International Standards Organization (ISO) and the American Conference of Governmental Hygienists (ACGIH), respectively.[11, 12, 13] The set is often referred to as the ‘CEC/ISO/ACGIH criteria’. Each of the individual criteria listed is expressed in terms of a probability (i.e., of inhalation or penetration) as a function of particle aerodynamic diameter. Thus each may be described by a curve, as already mentioned, and the agreed versions for the three fractions listed above are shown in Figure 3. Also shown there are the aerosol (or particulate matter) fractions defined by the United States Environmental Protection Agency (EPA); namely, PM$_{10}$ (which is a definition for the thoracic fraction, but where the fraction is defined by a curve that is slightly different especially at the larger-particle end) and PM$_{2.5}$ (a more recent addition, aimed at separating out combustion-related aerosols in ambient atmospheric air).[14, 15] Following the rationale outlined above, such curves become the yardsticks against which the measured sampling efficiency performance data for candidate sampling instruments should be compared. That is, for a given fraction, the performance curve for the ideal sampling instrument should match the curve defining the criterion. Here the definition of what is and what is not a ‘match’, takes into account both the proximity of the instrument's performance curve to the curve representing the actual original criterion, along with considerations of how well the sampler collects the ideal mass.

![Figure 3: Summary of the latest, currently accepted, particle size-selective criteria for health-related aerosol exposure assessment.[17]](image_url)

The fractions described above would appear to be sufficient for the needs of most standards. However it is important to note that none of them actually defines a fraction that relates directly to...
dose. That is, they refer to penetration to a given region of the respiratory tract, and hence not necessarily to what is actually deposited. For the purpose of some epidemiology, it has been argued that it would be more appropriate to define a deposition fraction. For example, McCawley has advocated an alveolar deposition fraction that is more directly related to dose than the penetration-based respirable fraction.[16] The same rationale may be extended to other fractions, including ones for very fine and ultrafine particles that are currently not embodied in the CEN/ISO/ACGIH criteria.

As discussed in a recent book by this author,[17] a rich source of information on which to base any extension of the currently-accepted set of particle size-selective criteria may be found in the comprehensive 1994 report of the International Commission on Radiological Protection.[18] This report describes how all human lung deposition data available at the time were modeled to provide a large set of empirical equations for the specific deposition efficiencies for each region of the respiratory tract, and for particles both in the aerodynamic and thermodynamic regimes respectively. These equations may be used in turn to determine the deposition efficiency (as a proportion of what was inhaled in the first place) for particles of all sizes in any region of the human respiratory tract, taking into account particle deposition occurring during both the inspiration and the expiration phases of the breathing cycle. Once the deposition efficiency is calculated in this way for representative breathing conditions (e.g., corresponding to nose or mouth breathing, corresponding to level of work activity undertaken, etc.), a curve representing a criterion for specific applications may be created, and – in turn – an appropriate sampling instrument may be sought, either an existing instrument, modified accordingly, or one designed from scratch.

There are at present no health-related particle size-selective criteria for ultrafine particles in the range of diameter below 0.1 μm. But, because of the interest stimulated by concerns about health effects in populations exposed to ultrafine particles in working and ambient atmospheric environments, much current research is striving to provide the information needed in order to develop a standard. Some of the more recent developments will be described elsewhere at this Symposium. In order to establish a firm scientific basis for criteria for ultrafine aerosols, and subsequently exposure assessment, there are several issues that need to be addressed and integrated. In the first instance they must include the particle size-dependent deposition of ultrafine particles in relevant regions of the respiratory tract. It is generally believed that there are two significant target regions of the human respiratory tract for particles in this size range, the nasal passages (for nose breathing) and the alveolar region (for mouth breathing). There are thought to be distinctly different, potentially-serious, health effects thought to arise from deposition of ultrafine particles in both of these regions. This awareness provides a useful starting point, suggesting the need for two criteria for ultrafine particles. For ultrafine particles, however, it is not possible to separate the criteria from the methods by which the sampled particles are assessed. Although, as described earlier, there are data for the particle size-dependent deposition efficiency of very small particles in the nose and alveolar region, we are not yet sure of the manner in which particle size influences the nature and level of the toxic response. In turn, therefore, we are uncertain about the most appropriate metric for aerosol concentration. From inhalation toxicology, \textit{surface area concentration} would appear to be more appropriate than the \textit{mass concentration} which is customarily applied nowadays for most aerosols.[19] Whichever is eventually deemed to be the most appropriate index of exposure concentration, however, it will remain necessary to integrate that knowledge with the deposition curve for either of the regions indicated in order that dose may be estimated. It is worth summarizing how this might be achieved.

Based on the equations for nasal and alveolar deposition for very fine particles presented in the ICRP report, we may develop the deposition criteria, say, \( UN(d) \) and \( UA(d) \), respectively (where \( d \) is now the thermodynamic particle diameter. The particle equivalent volume diameter is usually considered appropriate for this). Here it is noted that special care should be taken in choosing the most appropriate representative breathing flowrate, since inspiration through the nose usually takes place only at lower volumes corresponding to relatively light work. Popular current instrumentation for evaluating ultrafine aerosols is the differential mobility analyzer (DMA), which provides the particle
size distribution – say \( f(d) \) – of the aerosol in the size range of interest. It is therefore a simple matter to apply such information directly in one or other of the following

\[
Dose(d_v^{\text{nasal}}) = f(d_v)UN(d_v) \quad \text{and} \quad Dose(d_v^{\text{alveolar}}) = f(d_v)UA(d_v)
\]

That is, the measured particle size distribution is combined mathematically with the fraction of interest, leading to an accurate estimate of what is actually deposited. Scientifically, it is not sufficient to simply define and measure ultrafine particles as those below a certain size (e.g., 0.1 \( \mu \text{m} \), as has been suggested as one possible threshold).

6. Conclusions
This paper has argued that due attention to the correct definition of exposure, coupled with a full understanding of the basis of exposure assessment as it might be applied in the context of either standards or epidemiology, can provide the most representative measure of aerosol exposure relevant to specific health effects. A framework exists by which to draw together the contributions of the individual disciplines that are brought to bear in dealing with the behaviour and effects of inhaled particles.

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