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RADIATION SAFETY ASPECTS OF NANOTECHNOLOGY

National Council on Radiation Protection and Measurements

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Radiation Safety Aspects of Nanotechnology

Recommendations of the
NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS

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National Council on Radiation Protection and Measurements
7910 Woodmont Avenue, Suite 400 / Bethesda, MD 20814-3095

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Preface

The National Council on Radiation Protection and Measurements (NCRP) has provided guidance on operational radiation safety programs that involve the use of radionuclides in medicine, educational institutions, research laboratories, nuclear power plants, commercial industries, astronaut space missions, security screening in public locations, in potential acts of radiological or nuclear terrorism, and in protection against environmental contamination with radioactive materials. This guidance can be found in the following NCRP reports:

- Report No. 88, *Radiation Alarms and Access Control Systems* (1986);
- Report No. 116, *Limitation of Exposure to Ionizing Radiation* (1993);
- Report No. 125, *Deposition, Retention and Dosimetry of Inhaled Radioactive Substances* (1997);
- Report No. 127, *Operational Radiation Safety Program* (1998);
- Report No. 134, *Operational Radiation Safety Training* (2000);
- Report No. 156, *Development of a Biokinetic Model for Radionuclide-Contaminated Wounds and Procedures for their Assessment, Dosimetry and Treatment* (2006);
- Report No. 157, *Radiation Protection in Educational Institutions* (2007);
- Report No. 161, *Management of Persons Contaminated with Radionuclides* (2009);
- Report No. 162, *Self Assessment of Radiation-Safety Programs* (2009);
- Report No. 173, *Investigation of Radiological Incidents* (2012); and
- Report No. 175, *Decision Making for Late-Phase Recovery from Major Nuclear or Radiological Incidents* (2014).

This Report represents an important extension of guidance for radiation safety programs that involve the production and/or use of nanomaterials. Nanomaterials are considered to consist of particles of a size having at least in one dimension between ~1 and 100 nm. Nanoparticles (NP) occur naturally in sources such as sea spray, volcanic emissions, smoke from forest fires, and the decay of radon gas into nongaseous decay products. In recent years, engineered NPs, including those that are radioactive, have been developed and incorporated into a wide variety of engineered nanomaterials. These engineered nanomaterials are being used in a broad range of medical, industrial, educational,

and consumer products and their use is rapidly expanding. The increasing use of nanotechnology has been paralleled by concerns around health, safety and environmental impact. Nanotechnology was highlighted as one of the important NCRP initiatives at the 50th Annual Meeting in Bethesda, Maryland on March 10, 2014.

This Report describes the current state-of-knowledge relating to nanotechnology that is relevant to radiation safety programs. The Report considers operational health physics practices that may need to be modified when nanotechnology is involved and those that can continue to be performed in the traditional manner. Specifically, this Report provides guidance on contamination control, engineered and administrative controls, personal protective equipment including respiratory protection, training, waste disposal, and emergency response. The Report includes specific guidance for conducting internal dosimetry programs when nanomaterials are being handled.

Knowledge gaps are identified that should be filled in order to more effectively implement a comprehensive radiation safety program that includes nanotechnology.

This Report was prepared by Scientific Committee 2-6 on Radiation Safety Aspects of Nanotechnology. Serving on the Committee were:

Mark D. Hoover, *Chairman*
National Institute for Occupational Safety and Health
Morgantown, West Virginia

David S. Myers, *Vice Chairman*
Livermore, California

Members

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Los Alamos National Laboratory
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The Council wishes to express its appreciation to the Committee members for the time and effort devoted to the preparation of this Report.

NCRP also thanks the Health Physics Society for financial support contributed during preparation of the Report and the Centers for Disease Control and Prevention (Grant 5UE1EH000989). It goes without saying that the Council could not address the radiation protection needs of the nation without such willingness to contribute time and resources.

John D. Boice, Jr.
President

Contents

1. Executive Summary

1.1 Background

Nanotechnology is the understanding, engineering, control and use of matter at the nanoscale (*i.e.*, dimensions between ~1 and 100 nm) where unique phenomena enable novel applications. In recent years, an increasing variety of nanomaterials have been developed and manufactured. These engineered nanomaterials are being used in a broad range of medical, industrial and consumer products; and their use is rapidly expanding. The increasing use of nanotechnology has been paralleled by concerns around health, safety and environmental impact. In particular, there is a focus on the potential for nanomaterials to be dispersed as nanoparticles (NP) that may be more reactive in biological systems (due primarily to the large ratio of particle surface area to particle mass for smaller particles). There are also concerns that NP may undergo unique particle-cell interactions, including cell entry and translocation across organ membranes, not possible for larger particles. To address such concerns, significant national and international efforts are continuing both to investigate the toxicity of nanomaterials (*i.e.*, nanotoxicology) and to provide guidance on appropriate standards and practices for protection of workers and members of the public. As noted in Section 6 of this Report, much has been accomplished in the last decade to understand the biological behavior of nanomaterials, but there are still areas of uncertainty as the field is still evolving.

The production and use of radioactive engineered nanomaterials is not currently extensive, but the types and applications are growing in number, particularly in medical applications. There is also a growing awareness that some existing processes within the nuclear and other related industries may also generate nano-sized radioactive materials. Although general health and safety guidance for nanomaterials are clearly relevant to such materials, there is a lack of specific guidance on appropriate radiation safety practices for radioactive nanomaterials. The purpose of this Report is to provide such guidance.

1.2 Scope

This Report is intended primarily for operational health physicists, radiation safety officers, and internal dosimetrists who are responsible for establishing and implementing radiation safety programs involving radioactive nanomaterials. It should also provide useful information for workers, managers and regulators who are either working directly with or have other responsibilities related to work with radioactive nanomaterials.

Specifically, this Report provides information and guidance on the following topics:

- definition of nanotechnology and nanomaterials;
- types and sources of nanomaterials, including naturally occurring, incidentally produced, and engineered;
- types, sources and applications of radioactive nanomaterials;
- nonradiological hazards of radioactive nanomaterials;
- elements of a standard radiation safety program, including internal dosimetry, that might require modification when handling radioactive nanomaterials, especially situations where the nanomaterials may be dispersible as NP; and
- appendices on radiolabeled nanomaterials, biokinetic models, and behavior of airborne NP.

1.3 Conclusions and Recommendations

1.3.1 *General*

The potential radiological hazard of radioactive nanomaterial should be considered within the context of the overall hazard posed by the material. Because of the uniqueness of some of the nonradiological hazards associated with nanomaterials and the remaining uncertainties, the radiation safety program should be coordinated with other occupational health disciplines (*e.g.*, industrial hygiene, occupational safety) so that all the potential hazards are adequately addressed.

In addition to standard radiation safety training requirements, training should address any unique characteristics and safety considerations related to radioactive nanomaterials.

1.3.2 *Operational Health Physics*

There are three important factors that operational health physicists need to consider when radioactive nanomaterials are being used:

- potential physicochemical toxicity of the radioactive nanomaterials may lead to exposure limits that are lower than those associated with the radioactivity alone;
- potential differences in the behavior of radioactive nanomaterials within the human body may impact how internal radiation dose is assessed and controlled; and
- potential differences in contamination control and measurement procedures, as nano-sized materials may behave differently than materials of larger particle size within the work environment.

Most of the elements of a standard radiation safety program for handling radioactive material are directly applicable to radioactive nanomaterials. Of special note are the following:

- The ventilation currently used to control exposures to gases, vapors, and airborne particles in general is sufficient to control exposures to radioactive nanoparticles (RNP). New laboratory hoods based on low-flow and/or low-turbulence enclosures reduce the inadvertent loss of material during the handling of nanomaterials in powder form. Ventilation rates for gloveboxes and hoods should be properly adjusted during the handling of NP to minimize the potential for the spread of contamination both inside and outside of these enclosures. In general it is recommended that for radioactive nanomaterials guidance on local exhaust ventilation (LEV) for radioactive materials be considered in conjunction with that for nanomaterials in general in order to determine the appropriate type of LEV for the activity.
- The respiratory protection equipment currently available to control exposures to gases, vapors, and airborne particles in general is sufficient to control exposures to RNP. Careful attention should be given to properly maintaining and fitting respirators, as leakage past face and respirator cartridge seals is a concern for particles of all sizes.

Minor modifications are required for some program elements, primarily where potential exists for dispersion of RNP. Specific issues include the following:

- Preferential consideration should be given to the use of workplace clothing made from low dust-retention and low dust-release fabrics, such as polyethylene textiles, as there is an increased possibility that nanomaterials may penetrate

anti-contamination clothing that is made of woven fabric material.
- Contamination control programs for processes involving nanomaterials should consider the potential for wider contamination spread whenever dispersible materials are being handled.

Theoretical and experimental studies have indicated that filters typically used in LEV systems and respiratory protection equipment are effective filters for NP. It is generally recommended that high-efficiency particulate air (HEPA) filters be used in local containment system exhausts where unsealed highly radiotoxic material or radioactive materials in a dispersible form are used, and this clearly applies to radioactive material in nanoform as well.

The use of radioactive nanomaterials may under some circumstances require additional contamination measurement activities beyond those generally used to determine or confirm particle characteristics (*e.g.*, NP aerosol size analysis), primarily in support of internal dosimetry calculations. Such activities use sophisticated equipment and it is recommended that such measurements be conducted by specialists with suitable expertise.

1.3.3 *Internal Dosimetry*

The radiation safety program element that could potentially require the most attention due to the use of nano-sized radioactive material is internal dosimetry. Because internal dosimetry is best accomplished through the use of material-specific particle size and bioassay parameters for the actual materials being encountered, it will be important to measure and understand existing gaps in knowledge about the biological behavior of both current and emerging nanomaterials. In this Report, the impact of exposure to RNP versus other sized radioactive materials has been considered from the viewpoints of:

- route of intake (*i.e.*, inhalation, ingestion, wound, dermal);
- biokinetic behavior in the intake tissues and organs as well as the systemic organs after reaching the blood; and
- the selection and description of target organs and tissues for calculating doses.

Accordingly, the following can be concluded based on present knowledge of RNP and current biokinetic/dosimetric models:

- For ingestion intake of RNP, the International Commission on Radiological Protection (ICRP, 2006a) Human Alimentary

Tract Model (HATM) appears to provide an adequate biokinetic and dosimetric model in that particle size is not considered an important factor influencing the distribution of radionuclides within the model's contents or the absorption to blood. Nevertheless, studies with ingested engineered nanomaterials have shown that transluminal transfer of particles, at least to the liver, can occur and may add a complexity to the biokinetics not observed with larger particles.

- For intakes *via* contaminated wounds, the National Council on Radiation Protection and Measurements (NCRP) wound biokinetic model (NCRP, 2006) appears to be adequate in structure and parameterization to accommodate the unique features of RNP for both biokinetics and dosimetry, although it is recognized that new parametric values may be required to better describe the biokinetics in humans.
- Although there are very good models by ICRP (1994a) and NCRP (1997) for describing the biokinetics and dosimetry of inhalation intakes of radionuclides, there are aspects of the models as they are currently configured that need to be considered in order to describe some of the unique features of inhaled RNP. Specifically:
  - The lack of appropriate regional deposition data, particularly for nano-sized particles, leads to significant uncertainty about where in the respiratory tract the particles will deposit. This is reflected, for example, by the more than twofold differences in predicted deposition fractions in the bronchi and in the pulmonary region for ICRP and NCRP models.
  - The recognized differences in rates and amounts of phagocytosis of NP by airway and alveolar macrophages versus larger particles result in different distribution and retention patterns in the respiratory tract, but particularly in the parenchymal region of the lung. Thus, the fate of RNP within the lung microstructure can be different from that of micrometer-sized particles, and lead to biokinetic/dose distributions that are different and not accounted for by current models.
  - Because of the differences in microscopic distribution of NP versus larger particles in the lung, it is not clear whether the current dosimetric model used in ICRP (1994a) is adequate. Similar to other radioactive materials, the microdosimetric aspects of exposures to RNP will depend on the location of deposition, the type and energy

of radioactivity, and the rate of removal. The deposition location and rate of removal may be different for NP.

- It is clear from experimental data that the rate of translocation, tissue distribution, and retention of RNP that reach the blood greatly differ from those for solubilized radionuclides. These differences cannot presently be taken into account by existing systemic biokinetic models and likely will require new approaches for modeling.

To address issues with the current models, this Report calls for investigations to better understand the behavior (*e.g.*, deposition, biokinetics) of radioactive nanomaterials in the body, and also makes the following specific recommendations:

- New transport pathways and rates for NP translocation across the air-blood barrier (ABB) need to be considered for inclusion in a new Human Respiratory Tract Model (HRTM).
- Accumulation of NP in secondary organs needs to be considered in an updated HRTM.
- The modeling of the systemic biokinetic behavior of RNP reaching the blood should be treated discretely from solubilized radionuclides in blood because the uptake, distribution and retention of particulate and soluble radionuclides systemically are very different.
- For chronic exposure conditions involving NP, the potential for the accumulation of poorly soluble NP in secondary organs (an important issue) should be addressed.

It is noted that in future dosimetric models, chemical and particulate dosimetry quantities and factors may need to be evaluated in addition to the more traditional radiological dosimetry quantities for nanomaterials. In addition, the possibility that biological effects may occur as a result of combined insults from the radiological, chemical and particulate properties of RNP should be investigated.

1.3.4 *Summary*

In summary, the majority of the elements of a standard radiation safety program for handling radioactive material are directly applicable to the handling of radioactive nanomaterials or are applicable with minor modifications in situations where potential exists for dispersion of RNP. The program element that could potentially require the most modification is internal dosimetry. It is believed the current models for performing internal dose calculations will generally be suitable; however, the possible differences in the biokinetic behavior of RNP may require the adjustment of uptake,

transfer and elimination parameters when performing internal dose assessments. Exposure situations involving NP should be assessed by obtaining and using material-specific information whenever possible. New research should be undertaken to address these biokinetic and dosimetric data needs. Greater experience in using radioactive nanomaterials may lead to revised NCRP guidance on the radiation safety aspects of nanotechnology, particularly in the area of internal dosimetry, in the future.

2. Introduction

The context of this Report is at the nexus of safety, health, well-being, and productivity; the management of risk; and the challenges and opportunities of an emerging technology (Figure 2.1). The development of this Report supports the premise for radiation protection in the 21st century that guidance should keep in step with the changing times, including the changes and development of new technologies in medicine, industry, and for societal uses (Boice, 2014).

2.1 Background

Nanotechnology is the understanding, engineering, control, and use of matter at the nanoscale (*i.e.*, dimensions between ~1 and 100 nm) where unique phenomena enable novel applications (NNI, 2012). Unique phenomena at the nanoscale include how light behaves in materials, how electricity is conducted, and how materials dissolve or interact with biological material. Those differences cannot be predicted as simple extrapolations of the properties of similarly-composed macro materials.

NP occur naturally in the environment in sources such as sea spray, volcanic emissions, smoke from forest fires, and in the decay of radon gas into nongaseous radon decay products. NP occur incidentally from human activities in sources such as welding fumes and engine emissions.

In recent years an increasing variety of engineered nanomaterials, including those that are radioactive, have been developed and manufactured (Chopra, 2011; Farokzad and Langer, 2009; Hodge *et al*., 2010; Schug *et al*., 2013; Singh, 2011; Tinkle, 2010). These engineered nanomaterials are being used in a broad range of medical, industrial, educational and consumer products; and their use is rapidly expanding. In some cases, radiation is being used to create or alter materials at the nanoscale (IAEA, 2005). Nano-engineered structural materials, metals, coatings, coolants, ceramics, sorbents, and sensors may be particularly useful in radiation-related applications (TMS, 2012). The National Aeronautics and Space Administration (NASA, 2015) has described the development of various types of nano-formulated low-cost, lightweight, and flexible radiation shielding to protect personnel and sensitive equipment from radiation damage in the complex environments

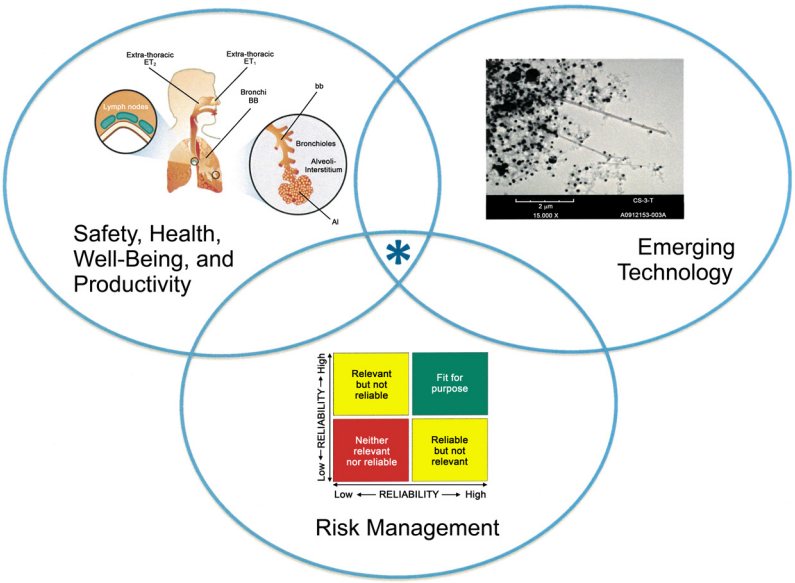


Fig. 2.1. Context of this Report on the radiation safety aspects of nanotechnology (Hoover *et al*., 2015).

of both human and robotic space exploration. Fadel *et al*. (2016) described applications of nanotechnology in advanced sensors, including for radiation.

Because the properties and behavior of materials at the nanoscale can differ from those of macro materials with the same constituents, it is important to understand the physical, chemical and biological properties of the nanomaterials directly. The physical and chemical properties that may impart unique characteristics to the behavior of engineered nanomaterials, especially in biological systems, include: particle size and size distribution, shape, surface area, charge, density, chemical compounds in the particle matrix and on its surface, dissolution behavior, and degree of agglomeration or aggregation. Although some information applicable to the radiation safety aspects of working with RNP has been derived from studying naturally occurring and incidental NP, questions remain about how traditional health physics program practices may need to be modified to provide adequate safety for working with radioactive nanomaterials or working with radiation in nanotechnology applications (Hoover, 2011a; Hoover *et al*., 2007; IAEA, 2005; Maiello and Hoover, 2010a).

2.2 Purpose

The primary purpose of this Report is to provide guidance on the radiation safety aspects of working with radioactive nanomaterials. Another purpose of this Report is to provide information on where the current and emerging applications of engineered radioactive nanomaterials in research and development, education, medicine, and industry may be occurring. This Report focuses on providing practical information to individuals responsible for establishing and implementing radiation safety programs, including operational health physicists, radiation safety officers, and internal dosimetrists. It also provides useful information regarding the safe handling of radioactive nanomaterials for workers, managers and regulators.

Finally, this Report should provide a useful resource for safety professionals responsible for the safe use of nonradioactive nanomaterials (*e.g.*, industrial hygienists) who may only be generally aware of the radiation safety issues that have to be addressed when working with radioactive nanomaterials. Although this Report focuses primarily on the radiation safety aspects of working with radioactive nanomaterials, it also provides guidance on assessing the overall potential hazard from radioactive nanomaterials, including physical and chemical hazards.

The Report covers the basic elements of a traditional radiation safety program. It summarizes those elements that are unlikely to require modification and focuses on those that may need revision based on the unique properties of nanomaterials.

3. Types and Sources of Nanomaterials Including Radioactive Nanoparticles

3.1 Introduction

Human beings throughout time have been exposed to ultrafine particles (*i.e.*, particles smaller than 100 nm in diameter). As shown in Table 3.1, the terms naturally occurring ultrafine particles, incidental ultrafine particles, and engineered nanoparticles (ENP) are sometimes used to differentiate between ultrafine particles that are naturally occurring from sources such as volcanic eruptions, ultrafine particles that are incidentally created during processes such as welding, and particles such as carbon nanotubes (CNT) or carbon nanofibers (CNF) that are "engineered" to be in the nanosized range.

As defined by the National Nanotechnology Initiative, the term nanotechnology refers to an emerging area of technology development involving the understanding and control of matter at the nanoscale (dimensions between ~1 and 100 nm) where unique

TABLE 3.1—*NP types by their mode of production (adapted from Kulinowski and Lippy, 2011a).*

NP Type	Examples
Naturally occurring ultrafine particles	• Volcanic ash • Sea spray • Forest fire combustion products
Incidental ultrafine particles	• Welding fumes • Engine emissions • Combustion products from propane vehicles and direct-gas heaters
Engineered (manufactured) NPs	• Nanotubes • Nanoscale titanium dioxide • Quantum dots

phenomena enable novel applications (NNI, 2012). Figure 3.1 illustrates the relative size of objects, including ENP in the size range of 1 to 100 nm having a wide variety of material morphologies and compositions. Figure 3.2 illustrates the many existing and emerging commercial applications of ENP. Sections that follow present additional details about naturally occurring, incidental and engineered nanomaterials, including radioactive nanomaterials.

3.2 Naturally Occurring and Incidentally Produced Nanomaterials

Nano-sized particles present in ambient air that are not deliberately manufactured are either naturally occurring from sources such as forest fires, volcanic action, or ocean spray, or incidentally produced in human activities such as engine emissions, combustion processes (*e.g.*, domestic solid fuel heating and cooking), and industry. The radioactive decay of radon gas also gives rise to nano-sized airborne particulates. Within urban environments the primary source of exposure to ultrafine particles comes from vehicle engine exhausts.

Particles can either be directly emitted into the air or be formed in the atmosphere from gaseous precursors (*i.e.*, secondary particles). Secondary particles are the products of atmospheric transformation of nitrogen oxides, mainly emitted by traffic and some industrial processes, and sulfur dioxide resulting from the combustion of sulfur-containing fuels. Furthermore, there are "secondary organic aerosols" formed by atmospheric photo-oxidation and subsequent polymerization of gaseous aromatic compounds. Secondary particles are mostly found in the fine particulate matter (PM) fraction of airborne particulate air pollution, generally referred to as $PM_{2.5}$ (*i.e.*, particles with size <2.5 μm). The mass concentration metric of ultrafine particles is generally defined as $PM_{0.1}$ (*i.e.*, mass concentration of particles with size <100 nm) or, on occasion, as $PM_{0.3}$ (*i.e.*, mass concentration of particles with size <300 nm) and are, clearly, a subset of $PM_{2.5}$.

As illustrated in Figure 3.3 for typical diesel-engine emissions, the particle size distribution of ambient airborne PM comprises a nuclei mode centered at ~20 nm, an accumulation mode centered at ~200 nm, and a coarse mode centered at ~5 μm (Finlayson-Pitts and Pitts, 2000; Kittelson, 1998; Kittelson and Watts, 2002). Although the nuclei mode contains the greatest number of particles, the mass of those ultrafine particles contributes little to the total mass of the diesel PM. Most of the mass of diesel exhaust is associated with the relatively fewer number of particles in the accumulation mode and with the relatively even fewer number of

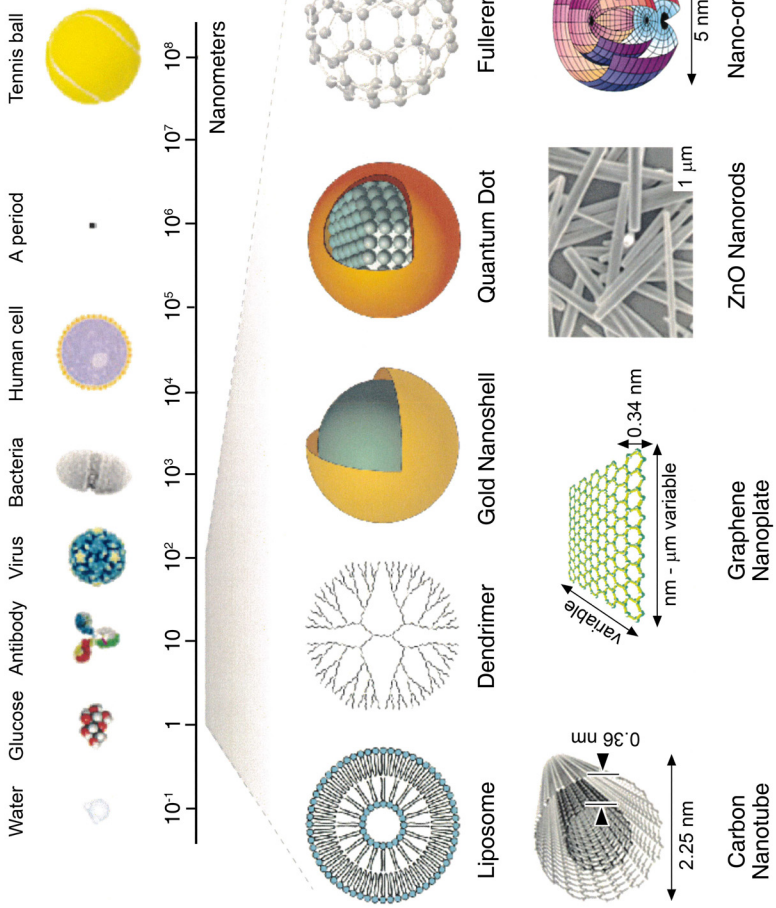


Fig. 3.1. Illustration of the relative size of objects including ENPs in the size range of 1 to 100 nm having a wide variety of material morphologies and compositions (adapted from McNeil, 2005; Oberdorster *et al.*, 2013).

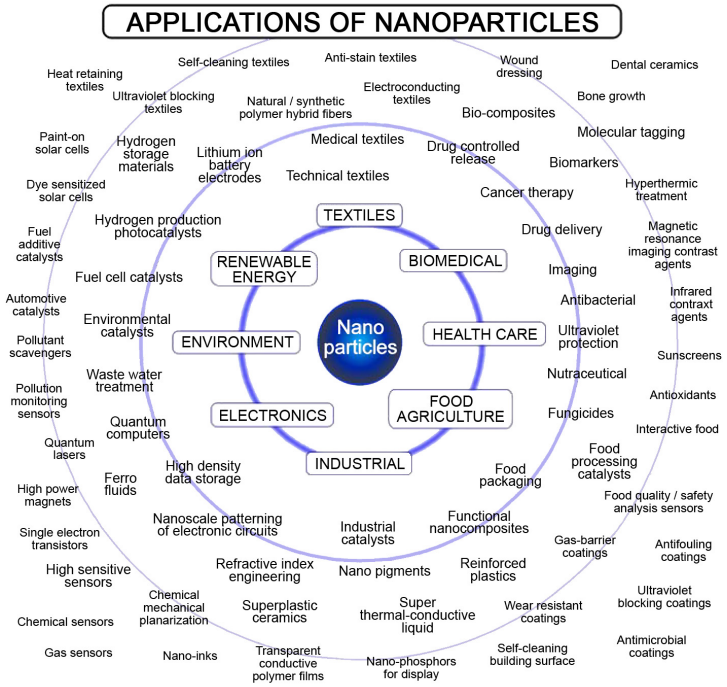


Fig. 3.2. Example commercial applications of engineered nanomaterials (Tsuzuki, 2009).

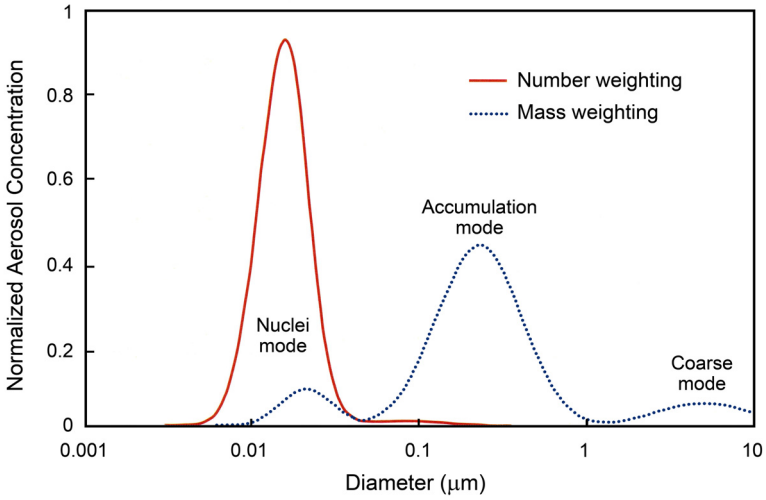


Fig. 3.3. Illustration of a distribution of diesel soot exhaust particles by number and by mass (Kittelson, 1998).

particles in the coarse mode. Ultrafine particle levels for ambient air pollution concentrations including diesel exhaust are therefore generally measured in terms of particle number concentrations (PNC). The results of a survey of typical measured PNC levels at roadsides in 42 cities across the world indicated an average PNC of $4.4 \pm 5.1 \times 10^4$ particles per cm^3 (Kumar *et al*., 2014).

Air pollution is clearly a significant public health issue. The World Health Organization (WHO) has estimated that air pollution contributes to 6.7 % of deaths worldwide (WHO, 2013). Epidemiological studies have consistently find associations between small increases in urban particulates and health effects, including increased morbidity and mortality from respiratory and cardiac disease (WHO, 2013). Susceptible groups with pre-existing lung or heart disease, as well as elderly people and children, are particularly vulnerable and reports such as from WHO (2013) indicate that there is no evidence of a safe level of exposure or a threshold below which no adverse health effects occur. These effects are epidemiologically associated primarily with exposure to $PM_{2.5}$; however, the role of the ultrafine fraction is as yet unclear. Recently, the exhaust from diesel engines, primarily particulate, was classified by the International Agency for Research on Cancer as carcinogenic to humans (IARC, 2012).

Other naturally occurring and incidentally produced nanomaterials include some minerals. These are formed by a variety of natural processes (Waychunas *et al*., 2009). For example, inorganic production of nanomaterials can occur in acid mine drainage sites, where iron-rich mine waters join oxygenated waters, forming iron-oxyhydroxide NP by hydrolysis. Similarly, weathering processes can extract metals and anions from rocks that may react at the surface to form NP that could enter streams or become airborne. Many types of clay are formed of nano-sized discs, and it recently has been postulated that such clay deposits may have been the birthplace of life on Earth (Yang *et al*., 2013). It also is clear that many biological processes can produce NP (Popescu *et al*., 2010), for example, zinc sulfide NP can be produced by microbial action and English ivy secretions from aerial rootlets contain an adhesive material composed of uniform sized NP (Lenaghan *et al*., 2013). These ivy generated NP are proteinaceous and it is likely that more such structures will be identified in the future. Many foods contain nano-sized structures, either naturally occurring or as a result of standard food processing procedures (*e.g*., casein micelles in milk products). Organic NP from natural food sources are generally assumed to present little or no health risk.

3.3 Radiation-Induced Synthesis of Nanomaterials

There are a number of mechanisms for radiation-induced synthesis of nanomaterials (*e.g.*, nano-structured glass, CNT, CNF, polymers, nano-metals, micro-devices, and micro-machinery) including the use of gamma irradiation, x rays, and electron beams (Huth, 2012; IAEA, 2005).

3.4 Radioactive Nanomaterials

Radioactive nanomaterials occur naturally in the environment, are produced incidentally within the nuclear industry, and can be engineered.

3.4.1 *Naturally Occurring Radioactive Nanomaterials*

The main source of naturally occurring radionuclide-containing nano-sized particles in the environment is the decay of radon gas to polonium and other nongaseous radon decay products. Radon is a naturally occurring radioactive gas that is emitted from the decay of radium in all rocks and soils. It is globally the largest source of naturally occurring radiation exposure of the population. The immediate decay products of radon gas are atoms of solid elements, themselves radioactive, which become attached to soil or other surfaces or emanate as individual atoms into the atmosphere. Initially the radioactive atoms rapidly coalesce with atmospheric gases and vapors to form molecular clusters in the size range 0.5 to 2 nm. These molecular clusters can then serve as nucleation centers for other atmospheric gases and vapors, growing to sizes of 2 to 100 nm. The molecular clusters and nucleation mode particles can then accumulate by attaching to other ambient particles in the air to form particle agglomerates in the size range of 100 nm to 1 μm. They can also attach to coarse particles in the air in the size range of 1 to 10 μm. Thus, measurements suggest that radon decay product activity is distributed across various size bands, typically classified as follows (Marsh and Birchall, 2000; Porstendorfer, 2001):

- molecular clusters (0.5 to 2 nm);
- nucleation mode particles (2 to 100 nm);
- accumulation mode particles (100 nm to 1 μm); and
- coarse mode particles (1 to 10 μm).

The typical radioactivity distributions of radon decay products as a function of particle size in different environments are shown in Figure 3.4. The standard convention for discussing human exposures to radon decay products is to refer to the amount of radioactivity in molecular clusters as the “unattached fraction” and the

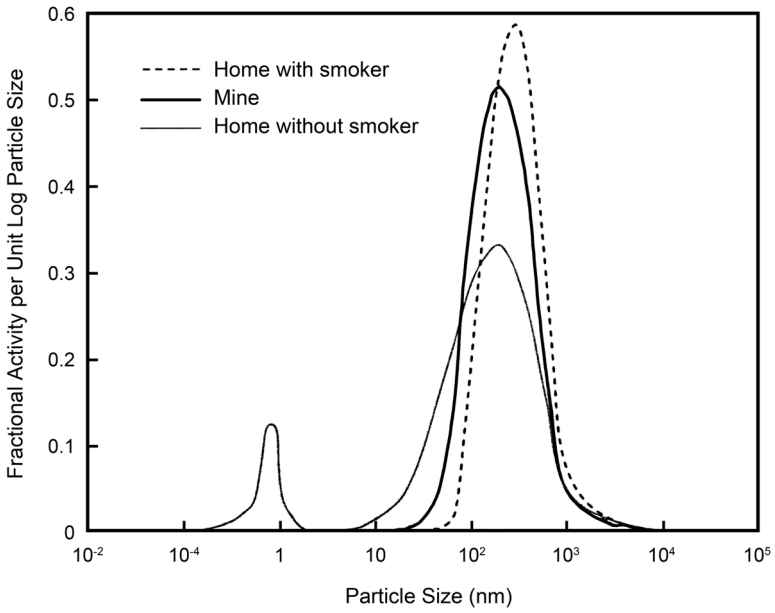


Fig. 3.4. Typical fractional activity distributions of radon decay products in different environments (Porstendorfer and Reineking, 1999).

sum of the radioactivity in the other modes as the "attached fraction." The distribution of decay product activity between particles of different size depends on environmental factors, including the concentration and size distribution of the ambient aerosol, the humidity, and any plate-out attachment processes (*e.g.*, to walls). In homes, values of the unattached fraction are typically 0.1, with lower values obtained if there is a smoker in the house, due to the high particle concentration in tobacco smoke. Note that although some of the radon decay product radioactivity in relatively dust-free environments such as homes without smokers remains as ultrafine molecular clusters in the "unattached" fraction, most of the radioactivity in the dustier environments of homes with smokers and mines is associated with particle sizes in the "attached" fraction.

The health risks from radon and the control of exposures of members of the public and workers have been dealt with extensively elsewhere (*e.g.*, ICRP, 2010; 2014; NA/NRC, 1999; NCRP, 1989a) and are outside the scope of this Report. However, it is recognized that techniques developed for measuring radon decay product aerosols may be of use in relation to the measurement of RNP aerosols.

In addition to radon decay products, other naturally occurring radionuclides are ubiquitous in the environment, so clearly some of the naturally occurring and incidentally produced nanomaterials may contain radionuclides. For example, volcanic ash, which has a nano-sized component, will contain primordial radionuclides. Plants take up cosmogenic and primordial radionuclides, and if they are later burnt some of these radionuclides will be contained within components of the smoke, including potentially nano-sized particles. This is true for example of cigarette smoke, which can contain measurable quantities of ^{210}Po (NCRP, 2009a), although there is little information available in the literature on the aerosol particle size fraction containing the radionuclide. Nevertheless, these are minor sources of exposure to radionuclide-containing nano-sized particles. As noted by NCRP (2009a) the annual effective dose from inhalation of ^{210}Po and other alpha-emitting radionuclides in cigarette smoke for a one-pack-a-day smoker (20 cigarettes) would range from 0.1 to 0.7 mSv with an average of 0.36 mSv, which is in addition to the annual effective dose of 2.28 mSv per individual in the U.S. population that results from inhalation of the ubiquitous radon and thoron background.

3.4.2 *Incidentally Produced Radioactive Nanomaterials*

There is some indication from the literature that nano-sized radioactive particles may be produced as a result of various processes within the nuclear industry. For example, Ettinger *et al*. (1972) detected ultrafine plutonium aerosols by autoradiography in glovebox areas of plutonium facilities; Raabe *et al*. (1978) reported the production of web-like chains of ultrafine crystalline (cubical) particles (4 to 100 nm on side) during the combustion of laser-ignited plutonium droplets in air; Newton *et al*. (1987) characterized the release of ultrafine metal-oxide aerosols during electric-arc and plasma-torch cutting of radioactively contaminated pipe; Dorrian and Bailey (1995) summarized particle-size distributions of radioactive aerosols observed in workplaces including ultrafine particles from the process for chemical recovery of plutonium (Elder *et al*., 1974) and from uranium processing plant activities involving sawing and oxide burner operations (Heid and Fuqua, 1974); and Cheng *et al*. (2005) identified nano-sized plutonium particles being produced by the plutonium material powering radioisotope thermal generators. These were interpreted as a gas-phase nucleation phenomena arising from internal sputtering. However, the overall extent of the incidental production of radioactive nanomaterials in the nuclear industry is unknown. It is possible that nano-sized par-

ticles may be produced as a result of nuclear accidents; however, it is likely that any such particles would become rapidly attached to larger ambient particles before significant populations could be exposed. For example, Masson *et al*. (2013) reports the results of the radioactive analysis of aerosols according to their aerodynamic size, which were performed in Austria, the Czech Republic, France, Germany, Greece, and Poland after the arrival of contaminated air masses following the nuclear accident at the Fukushima Dai-ichi Nuclear Power Station in March 2011. This report indicated typical activity median aerodynamic diameters (AMAD) in the hundreds of nanometers range. In the Capstone Project (Parkhurst and Guilmette, 2009) in which large-caliber depleted uranium (DU) projectiles penetrated DU or non-DU armor, electron microscopic and elemental analyses were done on aerosol samples taken within the crew compartments of Abrams tanks and Bradley fighting vehicles. The results showed that nano-sized aerosols were created, which consisted of the aluminum and iron components of the armor, but no DU NP were observed. The differential elemental behavior was attributed to the differences in boiling points for the various metals, with that of DU being higher than the localized temperatures likely achieved during the armor penetration (Guilmette and Parkhurst, 2010; Krupka *et al*., 2009).

Interactions of the high-energy plasma in fusion-energy devices with the internal surfaces of the devices can result in the formation and release of particles that range in size from nanometers to many micrometers in diameter, including some particles that may be radioactive (Rosanvallon *et al*., 2009; Sharpe *et al*., 2002). Assessments and inhalation toxicology studies of particles of health concern in fusion reactor systems have addressed a range of materials from lithium and beryllium to heavy metals (Allen *et al*., 1986; Harmsen *et al*., 1984; Hoover *et al*., 1984; 1986). The amount and the physical and radioactive characteristics of the particles depend on a number of factors including the operational regime of the fusion device and the surface materials, structural materials, and heat-transfer materials used. The tritium within the plasma can also become trapped in the particles (Grisolia *et al*., 2015). Concerns that the proposed use of tungsten surfaces within the International Thermonuclear Experimental Reactor device may lead to the production of nano-sized tritiated particles with uncertain potential health risks have led to research to produce "model" tritiated nano-sized tungsten particles (Acsente *et al*., 2015), which can be used in toxicity and radiobiology studies. Ultrafine particles can also be formed by the spallation of materials such as tungsten or uranium that are used for beam stops in accelerator facilities. The

use of neutron or proton beams to evaluate the physicochemical properties of nanomaterials can also lead to activation of elements in those materials.

3.4.3 *Radiolabeled Nanomaterials*

A growing body of work involves the use of radionuclides to characterize and quantitate NP contents, to enable biokinetic and toxicologic investigations of the behavior of NP, and to conduct diagnostic medicine, medical imaging, and therapeutic medicine. Appendix A provides examples of how materials such as CNT and CNF, metals, polymers, and biological molecules are being created and used in those applications.

4. Physicochemical Concerns for Exposure to Nanoparticles

4.1 Nanoparticle Physicochemical Properties

The radiological aspects of RNP are considered in Sections 5, 6 and 7; however, the behavior and health effects of particles of all sizes including RNP are related to their physical and chemical (physicochemical) properties as well. Physicochemical properties that may impart unique characteristics to the behavior of engineered nanomaterials, especially in biological systems, include: particle size, size distribution, and degree of particle agglomeration or aggregation; particle shape, density, surface area, surface reactivity, charge, and nature of the chemical compounds in the particle matrix; particle dissolution behavior; and material dispersibility.

4.1.1 *Deposition Within the Respiratory Tract*

Particle size influences the mechanism and location of particle deposition within the respiratory tract. NP mainly deposit in the respiratory tract as a result of their diffusion properties, and diffusional deposition in a given airway is rather uniform. Impaction and gravitational sedimentation are the driving forces for the deposition of micrometer-sized particles. The inertial deposition of micrometer-sized particles (including NP agglomerates which may have diameters of hundreds of nanometer or larger) occurs preferentially at the bifurcations in conducting airways and can result in hotspots of deposition (Balashazy *et al*., 1999; 2003).

NP diffusional deposition depends on time and the displacement distance to the wall (ICRP, 1994a). Therefore, NP deposition increases with decreasing airway lumen size (*e.g*., bronchi to bronchioles) and finally within the alveoli. Yet, the deposited NP fraction in the periphery of the lungs decreases, since the aerosol concentration decreases with increasing depth into the bronchial tree due to previous NP deposition in the upper parts of the respiratory tract. Because the diffusional behavior of NP having a diameter of ~20 nm enables them to pass through the upper airways with minimal deposition, 20 nm NP have the highest alveolar

deposition probability. However, for NP < 20 nm the alveolar deposition decreases because their increasing diffusional deposition in the upper parts of the respiratory tract prevents them from penetrating deeper into the bronchial tree.

4.1.2 *Translocation Across Organ Membranes*

A unique feature of NP compared to micrometer-sized particles is that the small (*i.e.*, <100 nm) size of NP can result in distinct size-related particle-cell interactions, including cell entry and translocation across organ membranes. For example, although translocation of micrometer-sized particles across the ABB into blood and into lymph circulation does not appear to occur except under situations of high particle overload or other conditions involving damage or upset to lung and the integrity of the lung epithelial barrier, the translocation of NP across the ABB into blood and lymph circulation has (in contrast) been shown to occur in rodents even under conditions that do not involve particle overload. Donaldson *et al*. (2010) suggest the existence of a physiological clearance pathway for NP from the lung to the interstitium and across the visceral pleura into the pleural space, with subsequent uptake and clearance *via* lymphatic stomata of the parietal pleura. This pathway is of particular importance for situations in which fibrous particles reach the stomata openings but are too long to pass through the openings, and instead become lodged in the stomata openings where they can induce significant pathology ranging from inflammation to granuloma, fibrosis and mesothelioma. Petitot *et al*. (2013) investigated the respiratory deposition and translocation of uranium NP to secondary organs in rats. Although their study demonstrated that inhaled UO_2 NP could be translocated from the airways to the pulmonary interstitium and thereby reach the blood capillary vessels, the question remains open of whether the inhaled material crosses the barrier between lung tissue and the blood stream as solid NP or as soluble ions.

Gearhart *et al*. (1980) and Guilmette *et al*. (1987) have shown in dogs exposed by inhalation to plutonium particles (1.5 or 2.8 μm AMAD; 0.41 or 0.86 μm geometric diameters) that intact plutonium particles could be observed in liver and spleen, and that the number of intact plutonium particles in the liver and spleen increased monotonically with time after exposure. According to the authors, it was clear that significant radiation damage to the ABB caused by the presence of the alpha-particle-emitting plutonium particles enabled this translocation pathway. The authors also noted that it was not possible to differentiate between translocation pathways that involved either (1) penetration of particles

through the lung interstitium into blood capillaries or (2) uptake of particles into the tracheobronchial and mediastinal lymph nodes followed by movement to the thoracic duct and into the blood. Regarding the possibility that particles cleared to the gastrointestinal (GI) tract from the respiratory tract *via* the mucociliary escalator and swallowing might be a concern, there is no evidence for uptake of plutonium particles through the GI tract; in fact, the fractional uptake of soluble plutonium from GI tract to blood is only 10^{-6} to 10^{-5}.

Translocation of inhaled quartz particles to liver and spleen has also been observed in studies with nonhuman primates following chronic exposure to high concentrations of fine crystalline silica particles (Rosenbruch, 1990), as well as confirmed for humans in clinical pathology reports of silicosis in liver and even bone marrow following inhalation exposures to quartz (Eide *et al*., 1984; Slavin *et al*., 1985). While a lymph-to-liver transport from the lungs has been suggested as the underlying transport mechanism, the possibility of particle clearance and translocation from lung into the GI tract and subsequent uptake into lymph and blood circulation has to be considered as well. In general, evidence of NP translocation in large animal species is very limited (Brown *et al*., 2002; Mills *et al*., 2006; Moller *et al*., 2004; 2006; 2008; Nemmar *et al*., 2002; Wiebert *et al*., 2006a; 2006b). It should, however, be noted that the information about possible NP translocation reported in Nemmar *et al*. (2002) has not been confirmed. Additional information on animal models and particle translocation is provided in Section 6 and Appendix B.

4.1.3 *Surface Area and Reactivity in Biological Systems*

Nanomaterials also have the potential to be more reactive in biological systems due primarily to the large surface area to mass ratios for such materials. As illustrated in Table 4.1 and described further in Appendix C, particle surface area per unit of particle mass increases dramatically for very small particles.

4.1.4 *Particle Shape*

The importance of particle shape may be exemplified by long (*i.e*., >10 μm) biopersistent and rigid CNT. For example, multiwalled carbon nanotubes (MWCNT) with a diameter usually <100 nm or single-walled carbon nanotubes (SWCNT) with a diameter of <10 nm may cross important barriers including the alveolar-capillary and parietal pleural barriers and thereby gain access to multiple secondary organs (*e.g*., liver, spleen, bone marrow). There

TABLE 4.1—*Illustration of the influence of particle size on particle surface area, mass per particle, and relative particle surface area per unit mass.*

Particle Diameter (nm)	Relative Surface Area	Relative Mass	Relative Surface Area per Unit Mass
5,000	250,000	125,000,000	1
1,000	10,000	1,000,000	5
100	100	1,000	50
50	25	125	100
10	1	1	500

is experimental evidence that those long, biopersistent, rigid CNT cannot be completely phagocytized by phagocytes (frustrated phagocytosis) causing oxidative stress associated with respective markers and release of inflammatory mediators. This mechanism has long been known to be involved in the toxicity and carcinogenicity of long, biopersistent, rigid asbestos fibers, and it is possible that the processes for CNT damage to cells may be similar to those of asbestos which has been classified as a known human carcinogen (IARC, 1987). It has been shown that inhaled MWCNT can access intrapleural spaces from which long MWCNT cannot be cleared, and that the presence of MWCNT in the intrapleural spaces may lead to the formation of mesothelioma at the parietal pleura (Donaldson *et al*., 2010; Poland *et al*., 2008; Sakamoto *et al*., 2009; Takagi *et al*., 2008). However, these studies have been performed by direct intrapleural and intraperitoneal injection of high bolus doses in rodents, and those exposure conditions may not be relevant to actual exposures of humans. In addition, inhalation studies in laboratories have not confirmed these carcinogenic effects at this time. Kuempel *et al*. (2016) have provided a critical evaluation of the mechanistic evidence and key data gaps in assessing the potential carcinogenicity of CNT and CNF in humans. The International Agency for Research on Cancer (IARC, in press) in its most recent evaluation has determined that for only one type of MWCNT is there sufficient evidence of carcinogenicity in experimental animals to list that material as a possible human carcinogen (Group 2B), but that it is possible that SWCNT and other MWCNT may also be classified once more studies are conducted.

4.1.5 *Particle Agglomeration*

Aerosols are dynamic systems undergoing changes in size and concentration. This is particularly true for NP aerosols. The Brownian motion of air molecules causes NP to move *via* diffusion. Hence, this motion may lead to the coagulation of two primary NP forming a doublet NP held together by forces such as the van der Waals force. The coagulation of multiple NP leads to the formation of fractal structures, sometimes chain-like agglomerates. As a result, at aerosol concentrations $>10^7$ particles per cm^3 of air, the ongoing coagulation under the typical thermodynamic conditions of atmospheric aerosols does not allow the formation of a stable aerosol of NP for more than a few seconds (Hinds, 1982). This is due to rapid coagulation which leads to a shift in size distribution towards increasing NP sizes at the same time their concentration is rapidly decreasing. Due to this coagulation behavior, most occupational and ambient NP aerosols (representing aged aerosols of a few hours and more) may reach maximal concentrations of $<5 \times 10^5$ cm^{-3}. Key concepts for understanding NP aerosol properties are explored in detail in Appendix C.

4.1.6 *Material Dispersibility*

Particles of a material dispersed as an aerosol can move through the workplace and remain suspended in the air for periods that depend on their particle size. The extent to which a material can be dispersed by a mechanical process (such as scooping, pouring, mixing, sawing, grinding, vacuuming) depends on the form of the material (*e.g.*, solid, particles in a liquid suspension, "sticky" particles, or dry "dusty" particles) and the energetics of the process. Dispersion of particles from brittle solids such as ceramics can be greater during mechanical operations than from soft materials. As noted by Evans *et al*. (2013) in their investigation of the dustiness of fine and nanoscale particles, Liden (2006) has argued that dustiness is not an intrinsic physicochemical property of a material; rather it is a behavior that is influenced by the particle size distribution, humidity, and nature of the adhesive forces binding the particles within the powder. The attractive nature of van der Waals forces can make it difficult to disperse or dislodge particles (especially ultrafine particles) from surfaces or from an agglomerated state. Thus, smaller particles are not necessarily easier to disperse.

As further noted by Evans *et al*. (2013), while not a material property, dustiness is a property of a given powder that should be quantifiable (and reproducible) under a given controlled testing protocol. Thus, they and others have addressed a number of test methods to evaluate dustiness, some involving relatively low energy

motion such as measurement of airborne particles released from material placed in a rotating drum, and some involving more energetic processes such as air jets (Evans *et al*., 2013; 2014). In addition to measuring the dustiness for specific materials of interest under the controlled conditions of the dustiness tests, the ultimate goal is to be able to predict the amount, size, and other properties of particle release from materials and processes in actual workplaces.

4.1.7 *Material Surface Charge*

The distribution of electrostatic charges on NP can be material dependent (*e.g*., including from application of different coatings on the NP surfaces). In some cases the polarity of surface charge may be the same on all particles, thus causing the particles to repel and resist agglomeration. In other cases the polarity of NP surface charge may be opposite, causing the particles to be attracted to each other and to agglomerate. NP surface charges can be altered by the local relative humidity and how the NP are handled.

4.2 Nanoparticle Exposure Experiences Involving Humans

The possible consequences of uptake of a variety of naturally occurring and man-made NP into the human body from a toxicity standpoint have been reviewed (Buzea *et al*., 2007; Nel *et al*., 2006). As noted by Valsami-Jones and Lynch (2015) evidence for the acute toxicity from nanomaterials at realistic doses is limited and there is currently no consensus on the toxicity of nanomaterials. The consequences of exposure to NP are dependent on the form and composition of the nanomaterial involved as well as the quantity. In a small number of cases, large acute exposures or persistent chronic exposures to inadvertently generated NP have led to clinical conditions, including a variety of inflammatory and pulmonary diseases. To date however, reported evidence of human health effects from exposures to ENP has been limited and sometimes in error.

The following four experiences have been reported that were thought to be associated with health effects from NP exposures. These experiences illustrate some of the challenges of confirming the actual conditions, compositions, and consequences of exposures, and the extent to which they may (or may not) involve NP.

4.2.1 *Magic Nano® Event*

The household cleaning spray Magic Nano® (Kleinman GmBH, Germany) was associated with severe respiratory health effects in more than 100 customers. However, the German Federal Institute

for Risk Assessment investigated the event thoroughly and could not find any NP in the product. The manufacturer also claimed no content of NP since the product name was selected from the fact that the spray would form a very thin protective film on glass or ceramics. The Institute associated the health effects with the liquid constituents of the spray solution (BfR, 2006).

4.2.2 *Event in China*

In 2009, the *European Respiratory Journal* published a report on the death in China of several workers for which the authors claimed the causal effects were from NP (Song *et al*., 2009). Yet, international interrogations concluded that there was no formal proof that NP exposure at the workplace caused the observed pulmonary disease and deaths of several workers in a primitive workplace that lacked any safety measures but had high concentrations of gaseous and particulate compounds in the air. Electron-microscope images of lung tissue and chest fluid from the affected individuals remained inconclusive regarding the presence of any NP. The authors had drawn conclusions by analogy which was not scrutinized thoroughly enough by the editor and reviewers of the journal (Brain *et al*., 2010; ERJ, 2010).

4.2.3 *Nickel Sensitization Case*

Journeay and Goldman (2014) reported a case of nickel sensitization in a 26 y old chemist who worked in a laboratory that formulated polymers and coatings using silver ink particles. The powders used in the formulations were routinely weighed out and handled on a laboratory bench with no protective measures in place. When she later began working with a nickel NP powder, the chemist developed throat irritation, nasal congestion, post-nasal drip, facial flushing, and new skin reactions to her earrings and belt buckle, which are symptoms consistent with exposure to nickel. Dimitri *et al*. (2015) noted this case as an example of the fact that failure to use basic industrial hygiene precautions when working with any hazardous material in any form can have negative consequences.

4.2.4 *Polymer and Metal Fume Experience*

Fumes generated by heating of polymers such as polytetrafluoroethylene or metals such as zinc consist of ultrafine particles. The terms *polymer fume fever* and *metal fume fever* have been coined to characterize the fever chills associated with exposure to such fumes. The fever chills may also be accompanied by pneumonitis and pulmonary edema. It has been shown that lung injuries associated

with short, acute occupational exposures to such fumes normally occur without lasting effects, but that high-dose, acute exposure to these fumes can cause severe lung injury (Rosenstock and Cullen, 1986). In some cases, such exposures have resulted in death (Makulova, 1965). Late effects of repeated exposure have included pulmonary fibrotic reactions (Goldstein *et al*., 1987).

Following earlier identification of hazards from in-flight exposure to pyrolysis toxins (Ferin and Oberdorster, 1992a; Nuttall *et al*., 1964), Oberdorster *et al*. (1992) assessed concerns for exposures of astronauts to thermal degradation products that may arise from accidental fire or smoke during manned space missions. Animal studies revealed the extremely high toxicity of freshly generated polytetrafluoroethylene fumes whereas a decrease in toxicity of aged fumes was also noted. This and the fact that toxicity of the freshly generated fumes can be prevented by filtering the exposure atmosphere implies that the toxicity may have been due to the particulate rather than the gas-phase components of the thermal degradation products of the polymer (Oberdorster *et al*., 1992). Support for that hypothesis is provided by Lee *et al*. (1997) and Warheit *et al*. (1990) who suggested that ultrafine particles present in these fumes were responsible for the fume toxicity and that coagulation of these ultrafine particles with increasing fume age would lead to less reactive larger particles.

4.3 Guidance on Managing Physicochemical Concerns for Exposure to Nanoparticles

Management of the radiological risks posed by RNP is discussed in detail in Section 5 but consideration also needs to be given to the management of the physicochemical hazards. There exists a wealth of guidance on approaches to the management of hazards in the workplace to address the exposure control hierarchy (*e.g.*, HSE, 2012; NA/NRC, 2011; NIOSH, 2009; OSHA, 2002). Detailed information on hazard and risk assessment and control for specific chemicals also is available for a wide range of materials. The National Institute for Occupational Safety and Health (NIOSH) *Pocket Guide to Chemical Hazards* (NIOSH, 2007), for example, includes details of the hazards presented by a wide range of chemicals and outlines the appropriate control measures for each. This guidance is based in part on detailed occupational health guidelines for chemical hazards (NIOSH, 2007). Chemical specific guidance also is available from a number of web-based sources, including the Occupational Safety and Health Administration (OSHA, 1994; 2002) and the European Chemicals Agency (ECA, 2015a; 2015b). Safety data sheets containing hazard information

also are provided by chemical suppliers. Such chemical specific guidance in many cases includes occupational exposure limits. However, in a critical review of safety data sheets for engineered nanomaterials, Eastlake *et al*. (2012) noted that 67 % of the nanomaterial safety data sheets reviewed provided insufficient data for communicating the potential health and safety hazards.

In addition to the general guidance on chemical hazards mentioned above, there exists some specialized advice on the control of nanomaterials, particularly in the research environment (Dunn *et al*., 2013; HSE, 2013; NIOSH, 2009; 2012; 2013a; 2016; OECD, 2009; UKNPG, 2016). However, guidance relating to specific nanomaterials including recommended exposure limits (RELs) from NIOSH is limited [*e.g*., for nano TiO_2 (NIOSH, 2011) and for CNT and CNF (NIOSH, 2013b)].

Schulte *et al*. (2010) described the state of the art for development of occupational exposure limits for ENP. Kuempel *et al*. (2012) described opportunities to develop risk-based nanomaterial groups for occupational exposure control. Darquenne *et al*. (2016) summarized research needs for inhaled aerosol dosimetry and noted numerous gaps in knowledge that need to be filled regarding the fate of varied NP following their deposition in the respiratory tract.

In the area of workplace exposure assessment, Eastlake *et al*. (2016) described the refinement of the NIOSH-developed NP emission assessment technique into the nanomaterial exposure assessment technique. To document realistic occupational exposure experiences, Dahm *et al*. (2015) conducted a comprehensive evaluation of exposures in U.S. CNT and CNF facilities and described the occupational exposure environment in 14 facilities that produce carbon nanomaterials.

Erdely *et al*. (2016) drew on insights gained from evaluating occupational exposures to CNT and CNF and recommended an integrated approach to the evaluation of nanomaterial toxicity involving "exposure-informed hazard assessment" and "hazard-informed exposure assessment" as follows:

- market-informed identification of potential hazards and potentially exposed populations;
- initial toxicity screening to drive prioritized assessments of exposure;
- development of exposure assessment-informed chronic and sub-chronic *in vivo* studies; and
- conduct of exposure- and hazard-informed epidemiological studies.

Additional sources of information and guidance on the measurement and safe handling of nanomaterials include the American Industrial Hygiene Association (AIHA) (Brandt, 2010; Gao *et al*., 2014; Hoover and Rickabaugh, 2014; Hoover *et al*., 2011; Kulinowski and Lippy, 2011a) and its AIHA Nanotechnology Working Group (AIHA, 2015a; 2015b); the Nanotechnology Committee of the Health Physics Society (HPS, 2015); the *Nanoinformatics 2020 Roadmap* (de la Iglesia *et al*., 2011); and online resources provided by the *GoodNanoGuide* (GNG, 2015) and the *Nanomaterial Registry* (RTI, 2015). Also of interest are the National Nanotechnology Initiative's signature initiative on *Nanotechnology Knowledge Infrastructure – Enabling National Leadership in Sustainable Design*, and the signature initiative *Nanotechnology for Sensors and Sensors for Nanotechnology: Improving and Protecting Health, Safety, and the Environment* (NNI, 2015a; 2015b). Some guidance on prudent laboratory practices includes nanomaterials and radioactive materials within the overall context of managing chemical hazards (NA/NRC, 2011) but there is currently no specific guidance relating to the overall management of radioactive nanomaterials.

All of the above guidance is relevant to health physics practitioners working in settings where both nanomaterials and radiation sources, including radioactive nanomaterials are present.

5. Operational Health Physics in a Nanotechnology Environment

5.1 Introduction

The fundamental principles of radiation protection [*i.e.*, justification, as low as reasonably achievable (ALARA), and dose limitation], as outlined in ICRP Publication 103 (ICRP, 2007) and NCRP Report No. 116 (NCRP, 1993), clearly apply in nanotechnology settings where ionizing radiation sources, including radioactive nanomaterials, are used.

The fundamental principles of radiation protection are:

- *Justification*: Justify any activity that involves radiation exposure on the basis that the expected benefits to society exceed the overall societal costs.
- *ALARA*: Ensure that the total societal detriment from such justifiable activities or practices is maintained as low as reasonably achievable, economic and social factors being taken into account.
- *Dose limitation*: Apply individual dose limits to ensure that the procedures of justification and ALARA do not result in individuals or groups of individuals exceeding levels of acceptable risk.

In particular, the principle of optimization enables determination of the appropriate level of radiation protection based on a graded approach. For example, if a new operation with a high potential for significant radiation doses is being planned, then significant effort and expense would be justified to identify and implement dose-reduction methods. However, if an existing operation entails radiation exposures that are already low, then the dose reduction efforts would be proportionally lower. Most operations typically will fall between these extremes. As noted by NCRP (1998), "Perhaps the most important approach to achieving ALARA is creating the proper 'mind set' in managers, supervisors and workers so that they always ask if a particular level of exposure is necessary."

General guidance on the application of the ALARA principle is available from a number of sources (*e.g.*, EAN, 2016; ICRP, 2006b) and reports that deal with the application of the ALARA principle in a range of operational situations (*e.g.*, Munro, 2004; NCRP, 1990; 1994) are also available.

Health physics professionals and others involved in the control of radiation exposures within the workplace are familiar with the general application of radiation protection principles, including the classic ALARA tools of time, distance and shielding. As health physics is a mature discipline, advice on the application of these principles in the development and implementation of radiation safety programs is available from a broad range of sources. Such advice covers both general guidance (ICRP, 1997; NCRP, 1998; 2009b), detailed guidance for particular occupational settings [*e.g.*, educational institutions (NCRP, 2007), nuclear power plants (NCRP, 1994), medicine (ICRP, 2007; 2013; NCRP, 2010a)] and specific contexts [*e.g.*, alarms and access controls (NCRP, 1986), shielding (NCRP, 2004), and radiation exposure during pregnancy (ICRP, 2000; NCRP, 2013)].

To date, practical health physics guidance relating specifically to nanotechnology exposure potentials has been lacking. The objective of this section of the Report is to address this deficiency.

The majority of the current guidance on the control of exposures to radiation from micrometer-sized particles is directly applicable to the handling of radioactive nanomaterials. There are, however, three important factors that operational health physicists need to consider when radioactive nanomaterials are being used:

- potential physicochemical toxicity of the radioactive nanomaterials may lead to exposure limits that are lower than those associated with the radioactivity alone;
- potential differences in the behavior of radioactive nanomaterials within the human body may impact how internal radiation dose is assessed and controlled; and
- potential differences in contamination control and measurement procedures, as nano-sized materials may behave differently than materials of larger particle size.

5.1.1 *Attention to the Physicochemical Toxicity of Radioactive Nanomaterials*

The first factor that operational health physicists need to consider when radioactive nanomaterials are being used is the physicochemical toxicity of radioactive nanomaterials. Usually when working with radioactive materials, the radiation hazard is significantly greater than the physicochemical hazard. Thus, the control measures applied for the radiation source often provide adequate

protection from the physicochemical hazard. However, there are exceptions (*e.g.*, natural and low-enriched uranium) where the chemical hazard is limiting. For example, U.S. Department of Energy (DOE) guidance for uranium facilities (DOE, 2004a) indicates that chemical toxicity of uranium is a higher risk than the radiation risk for soluble uranium with enrichment of 10 % or less. In recognition of the greater ability of uranium inhaled in a soluble form to reach the kidney, the NIOSH REL of 0.05 mg m^{-3} for soluble uranium particles is a factor of four more stringent that the NIOSH REL of 0.2 mg m^{-3} for insoluble uranium particles (NIOSH, 2007).

As discussed in Section 4, there are gaps in current knowledge about the potential health hazards from exposure to many nanomaterials. This has led to the adoption of a "precautionary" approach in much of the current guidance on nanomaterial control in the occupational setting (*e.g.*, HSE, 2013; NIOSH, 2009; 2012; 2013b; Schulte *et al.*, 2016). Because research on the exposure and toxicology of nanomaterials is largely a work in progress, there are relatively few current recommendations of exposure limits for nanomaterials.

Based on the toxicologically relevant greater surface area available for free-radical production of nano-sized titanium dioxide particles compared to micrometer-sized particles (NIOSH, 2011), NIOSH has assigned a REL of 0.3 mg m^{-3} for ultrafine TiO_2, which is a factor of eight lower than the NIOSH REL of 2.4 mg m^{-3} for micrometer-sized TiO_2. In comparison, OSHA has set the permissible exposure limit for TiO_2 at 15 mg m^{-3}, based on the airborne mass fraction of total TiO_2 dust (OSHA, 2014). Given a specific activity value of 0.17 Ci g^{-1} for ^{44}Ti and a radiation-based airborne exposure limit of 1×10^{-8} μCi mL^{-1} for oxides of ^{44}Ti (NRC, 2015), the corresponding mass-based exposure limit for $^{44}TiO_2$ is only ~0.06 μg m^{-3}, with the exact value increasing as the mass fraction of radioactivity in the compound decreases.

Based on its review of research studies with rodents in which adverse lung effects (including pulmonary inflammation and rapidly developing, persistent fibrosis) have been observed at relatively low-mass doses of CNT and CNF, NIOSH has assigned a REL of 1 μg m^{-3} for CNT and CNF (NIOSH, 2013b). In comparison, the OSHA (2014) permissible exposure limit for natural graphite is 15 mg m^{-3}. Given a specific activity value of 4,460 mCi g^{-1} for ^{14}C and a radiation-based airborne exposure limit of 1.0×10^{-6} μCi mL^{-1} for ^{14}C-labeled compounds (NRC, 2015), the corresponding mass-based exposure limit for ^{14}C is only ~0.2 μg m^{-3}, with the exact value increasing as the fraction of radioactive carbon atoms in the compound decreases.

Controlling exposures based on radiation exposure limits will likely maintain mass-based exposures below recommended limits. Nevertheless, the selection of appropriate control measures for radioactive nanomaterials should be driven by considerations of both their potential physicochemical hazard as well as their radiation hazard. For this reason, it is important that health physics professionals be aware of the control measures recommended for nonradioactive nanomaterials. Given this, it is expected that there will be a greater need for collaboration with other occupational health specialists with expertise in general nanomaterial safety. There is significant international research underway to establish the hazards and risks presented by nanomaterials. It is clear that nanomaterial safety is an evolving field and it is important to keep up-to-date with developments in this area. Recommended controls for nanomaterials are considered and their applicability to radioactive nanomaterials is discussed further in this section.

5.1.2 *Changes that May be Needed for Internal Dosimetry*

The second factor that operational health physicists need to consider when radioactive nanomaterials are being used is related to changes that may be needed for internal dosimetry because of differences between the deposition patterns and behavior within the body of nano-sized particles compared to those of micrometer-sized particles. This issue is discussed in Section 6 and the concomitant implications for bioassay are discussed in Section 7.

Differences in internal dosimetry would not be expected to lead to significant changes in operational practices, which are based primarily on the ALARA principle and the application of professional judgment. However, dose coefficients for intakes of radioactivity are sometimes used as an input for implementing controls so any differences from standard dose coefficients for radioactive nanomaterials may have implications for operational practices.

Should the dose coefficients for nanomaterials vary significantly with particle characteristics, then additional monitoring and characterization may be required, in particular to measure particle size distributions. This will be of particular importance in response to accidental intakes. The potential need for additional material characterization is addressed in Section 5.2.3.4.

5.1.3 *Changes that May be Needed for Dispersion of Airborne Particles*

The final factor that operational health physicists need to consider when radioactive nanomaterials are being used is the potentially greater dispersion of airborne NP relative to larger particles.

Guidance on contamination control in relation to this issue is discussed in detail (Section 5.2.3.2).

5.1.4 *Summary of Radiation Program Elements Applicable to Working with Radioactive Nanomaterials*

A summary of the radiation safety program elements applicable to working with radioactive nanomaterials is provided in Table 5.1 and a flowchart for the selection of nanomaterial engineered controls is provided in Figure 5.1. The specific program elements that may need to be modified are identified and guidance on potential modifications is provided in Section 5.2. It is important to note that this Report does not describe in detail all of the operational radiation safety requirements for working with radioactive nanomaterials. Rather this Report builds upon the general radiation safety literature, in particular the general guidance in NCRP Report No. 127 (NCRP, 1998).

5.2 Hierarchy of Exposure Controls for Facility and Process Design

The importance of the design stage when developing a new facility or process cannot be overestimated, whether it be for a multi-building operation or a relatively simple process within an existing laboratory. Traditionally, "the hierarchy of exposure controls" has been used as a means of determining how to develop and implement facility designs and process controls that are feasible and effective. A representation of this hierarchy is provided in Table 5.2. The idea behind this hierarchy is that the control methods at the top of this list are potentially more effective and protective than those at the bottom. Following the hierarchy normally leads to the implementation of inherently safer systems, ones where the risk of illness or injury has been substantially reduced. While good facility and process design does not eliminate the possibility of accidental radiation exposure or contamination, the probability and magnitude of such occurrences can be minimized. Proper facility and process design is an effective approach to reducing occupational exposures, minimizing releases to the environment, and reducing operating expenses. This emphasis on good design is clear in general guidance on radiation safety (*e.g.*, NCRP, 1998) and reflects wider occupational health and safety principles such as "prevention through design" (ANSI/ASSE, 2011; NIOSH, 2013a; 2016).

The most effective means to reduce radiation exposure is clearly to eliminate the sources, or if this is not possible, to reduce or modify them. The second most effective option is engineered controls,

TABLE 5.1—*Guidance for implementation of radiation safety program elements in nanotechnology settings.*

Fundamental Principles	
Justification	Follow standard radiation protection[a] guidance (*e.g.*, ICRP, 2006b; NCRP,1998).
ALARA	Follow standard radiation protection guidance (*e.g.*, ICRP, 2006b; NCRP, 1990; 1994).
Dose limitation	Follow standard radiation protection guidance (*e.g.*, ICRP, 2006b; NCRP, 1993).
Engineered Controls	
Containment/isolation	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and consider enhanced mobility of NP (Section 5.2.2 and Figure 5.1).
Ventilation	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and consider enhanced mobility of NP (Section 5.2.2 and Figure 5.1).
Filtration of exhaust	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and note the use of HEPA[b] filters is appropriate for all materials, including nano-sized (see Section 5.2.2.3 for guidance).
Shielding	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and consider enhanced mobility and deposition potential of NP (see Section 5.2.2.4 for guidance).
External Radiation Exposure Control	
Dose guidelines	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998).
Dose control techniques[a]	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998).
External radiation dosimetry	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998).

External radiation monitoring	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and when developing and implementing a monitoring plan consider enhanced mobility of NP (see Section 5.2.3.3 for guidance).
Personal protective equipment	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) (see Section 5.2.4.1 for guidance).
	Internal Radiation Exposure Control
Exposure guidelines and reference levels	See Section 6 for discussion of internal dosimetry for radioactive nanomaterials. See Section 5.2.3.2 for discussion of the use of dose coefficients for area designation and controls.
Contamination control techniques	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and when developing and implementing contamination control consider enhanced mobility of NP (see Section 5.2.3.2 for guidance). Vacuum cleaners should be HEPA filtered.
Contamination monitoring	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and when developing and implementing a monitoring plan consider enhanced mobility of NP (Section 5.2.3.3 for guidance). To allow complete identification of hazard potential, note the need to undertake additional characterization of the nanomaterials, in particular if in aerosol form to determine particle size (see Section 5.2.3.4 for discussion).
Internal dosimetry	See Section 6 for discussion of internal dosimetry for radioactive nanomaterials. See Section 5.2.3.4 for guidance on nanomaterial characterization requirements for internal dosimetry.
Personal protective equipment	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and when choosing clothes and gloves consider the potential for greater penetration through woven material by NP (see Section 5.2.4 for guidance).

TABLE 5.1—(*continued*)

Respiratory protective equipment (type and filtration)	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and use filters appropriate for all materials, including nano-sized (see Section 5.2.4.2 for guidance).
Administrative Controls	
Training	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998) and note that training also should be provided relating to the "chemical" hazard presented by the nanomaterial.
Procedures	Follow standard radiation protection guidance (*e.g.*, NCRP, 1998).

[a]Example dose control techniques = time, distance, and shielding.
[b]HEPA = high-efficiency particulate air

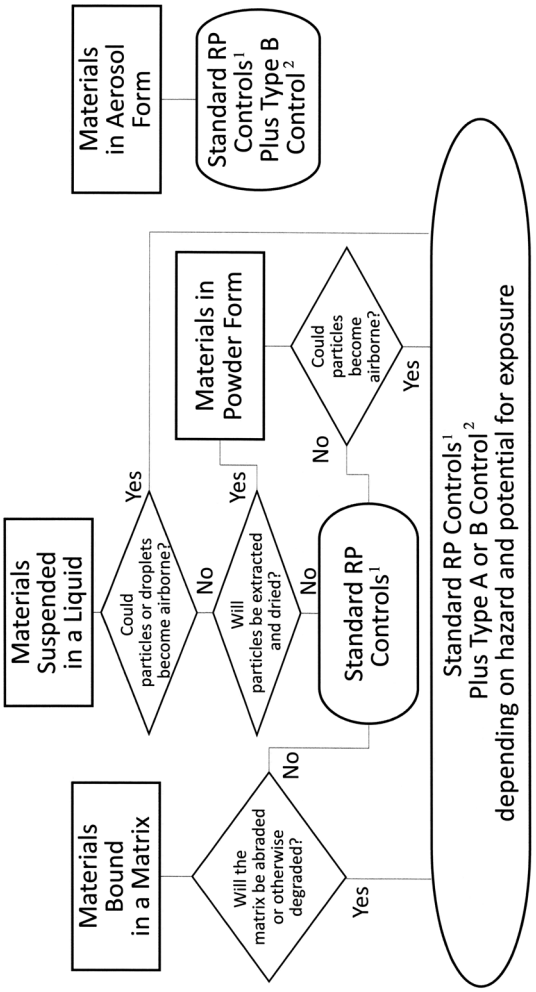


Fig. 5.1. Flowchart for the selection of nanomaterial engineered controls (adapted from UKNPG, 2016).

[1] Standard radiation protection (RP) controls apply in all circumstances where radioactive nanomaterials are used. They include appropriate use of time, distance and shielding; other administrative controls; and personal protective equipment.

[2] Type A control uses partial enclosure (*e.g.*, laboratory hood) with HEPA filtration of exhaust to a safe outside location. Type B control uses full enclosure (*e.g.*, glovebox) with HEPA filtration of exhaust discharged to a safe outside location. The need for Type A or Type B controls depends on the hazard and the potential for exposure (*i.e.*, material, quantity used, degree of encapsulation, activities undertaken). For example, large scale mechanical abrasion of items with radioactive nanomaterials bound in a matrix would be expected to require Type B, rather than Type A, control.

TABLE 5.2—*Hierarchy of exposure controls (adapted from NIOSH, 2009).*

Control Method	Process, Equipment, or Job Task
1. Elimination	Change design to eliminate hazard
2. Substitution	Replace a high hazard with a low hazard
3. Engineered	Isolation/enclosure, ventilation (local, general)
4. Administrative	Procedures, training, policies, work scheduling
5. Personal protective equipment	Respirators, clothing, gloves, goggles

which include the use of isolation, containment, appropriate ventilation systems, shielding, and access control systems. The application of these standard controls in handling radioactive nanomaterials is the primary focus of the following subsections.

5.2.1 *Elimination and Substitution*

Elimination and substitution, while most effective at reducing hazards, also tend to be the most difficult to implement in an existing process. If the process is still at the design or development stage, elimination and substitution of hazards may be inexpensive and simple to implement. For an existing process, major changes in equipment and procedures may be required to eliminate or substitute for a hazard. In workplaces where radioactive nanomaterials are to be produced or used (*e.g.*, processing, product manufacture, analysis, and testing) it is clearly not feasible to eliminate them. It may, however, be possible to change some of the aspects of the processes being used to reduce the potential for release of nanomaterials or the hazards presented. For example, in general, working with nanomaterials suspended in liquid is preferable to the use of dry powders.

If nanomaterials are being produced using a technique involving radiation or radioactive materials, then the potential for the replacement of the technique with another not resulting in radiation exposures should be explored. It is important to note, however, that the potential hazards of any other options (*e.g.*, physicochemical production processes) will need to be addressed in decision making on the most appropriate production process or technique. Also,

in evaluating the potential hazards of radioactive nanomaterials it should be noted that they are generally significantly easier to detect than nonradioactive materials which may help to limit potential exposures.

In cases where radioactive nanomaterials are being produced for specific purposes (*e.g.*, medical imaging) then the advantages of using nanomaterials against other comparable techniques should be considered as part of the overall justification process. It also is important to ensure that the level of radiation/radioactivity is the minimum required to perform the function. Processes that involve fewer opportunities for releases to the atmosphere generally are to be preferred over other processes. Considerations for proper waste disposal will also apply (Section 5.4).

5.2.2 *Engineered Controls*

Engineered controls are used to remove a hazard or place a barrier between the worker and the hazard. Well-designed engineered controls can be highly effective in protecting workers and will typically be independent of worker interactions to achieve this high level of protection. The initial cost of engineered controls can be higher than the cost of administrative controls or personal protective equipment (PPE), but over the longer term, operating costs are frequently lower, and in some instances, can provide a cost savings in other areas of the process.

Isolation and containment include the physical isolation of a process or piece of equipment either by locating it in an area separate from the worker or by placing it within an enclosure that will contain the hazard (*e.g.*, radiation source, radioactive materials, nanomaterials) to prevent or reduce exposure under normal conditions. Types of engineered controls that prevent or reduce exposure to airborne contaminants include gloveboxes, which isolate materials, and LEV systems (*e.g.*, laboratory chemical hoods, biological safety cabinets). Other engineered controls include shielding to reduce external radiation exposures and engineered access controls.

As emphasized above, engineered controls should generally be the primary means of controlling exposures, except in situations (*e.g.*, emergencies) where implementation of such controls may not be feasible.

The majority of the available guidance on the use of engineered controls in radiation safety (*e.g.*, NCRP, 1998) will be applicable in nanotechnology settings where radioactive sources including radioactive nanomaterials are used.

Control equipment, such as gloveboxes and LEV, are widely used to prevent or limit exposures to a wide range of other workplace

hazards and general guidance on their installation, operation and use will also be of relevance for nanotechnology settings using radioactive sources including radioactive nanomaterials. There is also a growing literature on the use of engineered controls within nanotechnology settings that will be of direct relevance to situations where radioactive nanomaterials are in use [*e.g.*, guidance on strategies for engineered controls in nanomaterial production and handling processes (NIOSH, 2013a)].

5.2.2.1 *Gloveboxes*. Gloveboxes allow the effective containment of nanomaterials. They should be operated under negative pressure to reduce potential leakage to a minimum. General guidelines on glovebox design and operation are available from a number of sources [*e.g.*, American Glovebox Society (AGS, 2007)] and specific advice on gloveboxes in nuclear applications is also available (*e.g.*, AGS, 2005; NVF, 2009). Other isolation containment systems that operate in a similar manner include glovebags (more flexible units) and some classes of biological safety cabinets (NIOSH, 2012).

It is important to ensure that the glovebox operating regime is appropriate for the purposes intended. A key factor to consider when using gloveboxes for nanomaterial containment is the fan operation rate. NP are potentially more mobile than larger particles and exhaust system fans operating at too high a rate might result in the NP becoming airborne and contaminating the internal surfaces of the glovebox and downstream components of the exhaust system, with implications for decontamination and external exposures, in addition to the loss of valuable working material. Consideration also needs to be given to potential accidental release conditions.

For accident conditions, guidelines for glovebox operation typically define an optimal breach velocity in terms of the velocity of the ingress air if the glovebox operates with one glove missing. Too low a velocity will increase the possibility of materials escaping from the glovebox as a result of air flows outside of the glovebox. Similarly, too high a flow rate may create turbulent flows within and around the glovebox, which again might facilitate the movement of nanomaterials from the containment. Typical guidance is that velocities of 0.64 ± 0.13 m s^{-1} (125 ± 25 feet min^{-1}) should be adequate to limit backflow in the event of a breach (*e.g.*, open glove port) (DOE, 2003), but that breach velocities >1 m s^{-1} can cause eddies and, hence, loss of protection (NVF, 2009). There is currently no specific nanomaterial guidance on breach velocities.

5.2.2.2 *Local Exhaust Ventilation*. LEV includes the widely used types of chemical hoods, and more specialized items including biological safety cabinets and powder handling enclosures. All can be

used to prevent or minimize exposure to radioactive nanomaterials. Guidance on the use of LEV with radioactive materials (NCRP, 1998; NVF, 2009) will in general terms be applicable in relation to radioactive nanomaterials. The specific choice of LEV will clearly depend upon the potential hazard presented, which is dictated principally by the operations planned and the type, form and quantities of material involved (Figure 5.1). There is no single preferred option. When determining an appropriate type of LEV for situations involving radioactive nanomaterials, it is recommended that the guidance on LEV for radioactive materials (NCRP, 1998; NVF, 2009) be read in conjunction with the guidance on LEV for nanomaterials (*e.g.*, HSE, 2013; NIOSH, 2009; 2012; 2013a; UKNSPG, 2012).

New laboratory hoods specifically designed for nanotechnology are being developed, including designs based on the low-flow and/or low-turbulence features of the "ventilated balance enclosures" used for handling potent powders in pharmaceutical applications. Such enclosures can reduce the inadvertent dispersion of material and thereby offer improved performance during operations such as weighing and mixing of NP powders (NIOSH, 2012; 2013a). Covello (2011) notes that the newer nanomaterial handling enclosures may also provide adequate containment at lower face velocities [*e.g.*, between 0.33 to 0.43 m s^{-1} (65 to 85 feet min^{-1})]. A recent evaluation of one such hood indicated generally good nanomaterial containment (NIOSH, 2013a). However, the study also reported that the effectiveness of the containment could be compromised by the operation of the air handling system (including air conditioning) in the room, indicating the importance of properly establishing and maintaining the overall room ventilation design for effective containment. Another recent hood design approach is the air-curtain hood (Huang *et al.*, 2007), which uses a downward air jet emanating from a double pane sash to isolate the interior of the hood from the exterior environment. An evaluation of the hood (Tsai *et al.*, 2010) indicated that it can be effective at containing airborne NP.

Recent research has shown that some laboratory fume hoods may allow the release of nanomaterials during their handling and manipulation (Tsai *et al.*, 2009). This research evaluated exposures related to the handling and manipulation of nanomaterial powders in three hood types: constant air volume, bypass, and variable air volume. This study showed that the constant air-volume hood, in which the face velocity varies inversely with sash height, allowed the release of significant amounts of NP during pouring and transferring activities involving nano-alumina. Sash heights both above and below the recommended height which produces a face velocity of 24.4 to 36.6 m min^{-1} (80 to 120 feet min^{-1}) (NIOSH, 2012) may

lead to increased potential for NP exposure for the user. In contrast, more modern hoods such as the variable air volume, which is designed to maintain hood face velocity in a desired range regardless of sash height, yielded better containment of NP than the other hoods tested.

These new developments in LEV design and procedures are in part a consequence of the need to limit inadvertent releases and the resulting occupational exposures but are also a reflection of the difficulty in handling NP within hoods. If the flow rates are too high or turbulent, simply opening a container of an easily dispersible NP can result in the rapid release of the material, with the air flow taking the material towards the exhaust, and with the potential for contamination of parts of the hood, in addition to the waste of a valuable resource. In some cases, chambers within fume hoods have been devised to reduce this possibility. Additional steps to reduce the potential to create turbulence when using nanomaterials in hoods include keeping the hoods as uncluttered as possible and having the operators remove their arms or other objects from the hoods very smoothly and slowly. Commercially available electrostatic discharge units can also be used to reduce the likelihood that the buildup of static charges on container surfaces or on the NP materials themselves will result in the inadvertent dispersion of NP during handling operations.

When working with radioactive materials, there might also be a need to include radiation shielding within the hood. Care should be taken to ensure that the positioning of the shielding does not compromise the containment properties of the hood by significantly affecting the air flow.

5.2.2.3 *Airborne Effluent Filtration*. It generally is recommended that HEPA filters be used to clean exhaust air from containment system and facilities where radioactive materials in a dispersible, or potentially dispersible, form are used (NCRP, 1998). This recommendation is equally applicable when the radioactive material is nano-sized. Note that HEPA filters are not suitable for cleaning radioactive gases or volatile organic radiochemicals (such as radioiodine) from the air, and that appropriate charcoal absorbers or chemical scrubbers should be used in such cases (NCRP, 1998).

A standard definition of a HEPA filter is one for which aerosol filtration efficiency is ≥99.97 % for particles of 0.3 μm diameter (DOE, 2005). High-efficiency filter performance is generally defined in relation to particles of ~300 nm, as this is typically the "most penetrating particle size" (MPPS). Theoretical models of filtration (*e.g.*, classical single fiber theory) predict the highest

filtration efficiencies for particles <20 nm and >1 μm in diameter (Figure 5.2), with the minimum filtration efficiency for particles around a few hundred nanometers in diameter (Hinds, 1999).

These theoretical predictions for the efficiency of particle collection by filtration have been confirmed by experimental studies (Kim *et al*., 2007; Wang, 2013). In addition, despite some suggestions that "thermal rebound" may reduce the capture efficiency of particles at very small sizes, a review by Givehchi and Tan (2014) of investigations in numerous experimental studies has shown no convincing evidence that thermal rebound plays a role in NP filtration. Thus, the collection efficiency of ≥99.97 % for HEPA filters should be effective for the filtration of airborne nanomaterials (NIOSH, 2009).

The above recommendation to use HEPA filters in glovebox and LEV systems designed to control potential exposures from dispersible RNP is consistent with general advice on nanomaterial control (NIOSH, 2012). It is also recommended that, wherever practicable, the exhaust should be filtered through a HEPA filter prior to venting to a safe place outside the building. Exhaust air should not be recirculated directly back into the workplace unless it has been

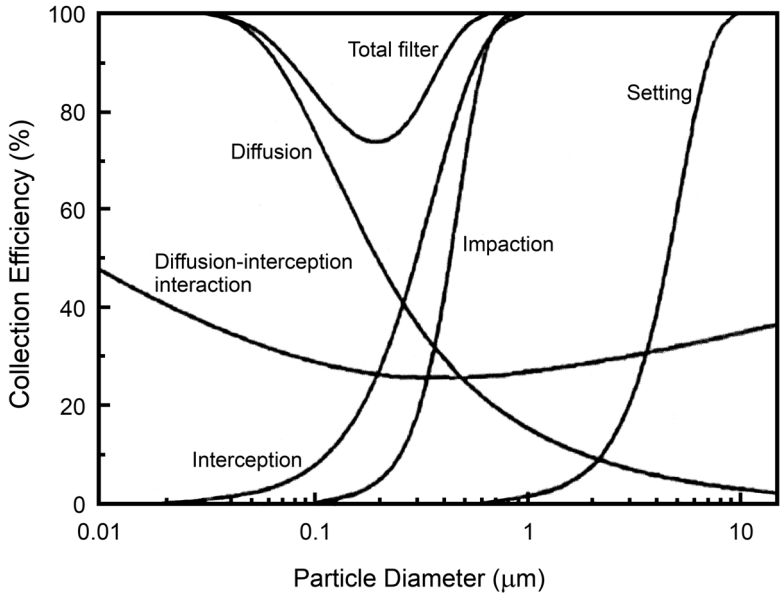


Fig. 5.2. Theoretical filter efficiency for individual single-fiber mechanisms and total efficiency (Hinds, 1999).

effectively filtered to remove airborne nanomaterials by at least one HEPA filter, except under exceptional circumstances (HSE, 2013; NA/NRC, 2011; UKNPG, 2016).

Clearly any filters used in an LEV system need to be coupled with well-designed filter housings that prevent the potential for filter bypass. This is of particular importance for NP because bypass leaks could potentially be of more consequence for particles with diameters near the MPPS than for smaller sized or larger sized particles (Mouret *et al*., 2009). Larger bypass leaks and mechanical or chemical damage to the filter media itself can allow the passage of particles of all sizes, rather than only those particles near the MPPS. Filters should be tested before initial use and periodically (*e.g*., every 12 months) and a routine filter replacement plan should be developed and followed. Procedures for contamination control during the changing of filters and their ultimate disposal will also be required. The likelihood of deposition of NP in the areas leading to the filter housing should be taken into account and thus extra care should be taken to prevent the transfer of contamination when undertaking any inspection, maintenance or replacement procedures.

5.2.2.4 *Shielding*. Clearly shielding is an important element of external radiation exposure control. In situations where radioactive nanomaterials are being used, it may be necessary to use shielding in addition to the other isolation and containment approaches listed above. Advice on appropriate shielding is available from a wide variety of sources (*e.g*., Shultis and Faw, 2010) and is not specific to the particle size. However, where nano-sized materials are in use their potentially enhanced mobility may require shielding across larger areas.

5.2.2.5 *Access Control Systems*. In facilities where radioactive nanomaterials are received, produced, handled or stored, access should be controlled to areas where radioactive contamination, elevated radiation dose rates, or elevated concentrations of airborne radioactivity could be encountered. Access control systems can include engineered controls such as warning signs, warning lights, audible signals, and physical barriers. Access control systems can also include administrative controls such as training (Section 5.3) and safety and operating procedures.

The use of appropriate labeling and safety signs for radiation sources, radioactive materials and chemicals is a regulatory requirement. Currently many nations are working toward a hazard labeling system for chemicals, which is in line with the *Globally Harmonized System of Classification and Labeling of Chemicals*

(UN, 2013). It is important to note that there is no standardized national or international approach to labeling specifically for nanomaterial hazards, beyond the standard chemical hazard approach. Typically, labeling requirements and hazard signage for radiation and chemical hazards will be specified by separate regulatory regimes. It will therefore be important to consider the full range of applicable regulatory requirements when determining appropriate labeling and safety signs for radioactive nanomaterials.

In general the selection of appropriate hazard labels or signs should be based on the available hazard information for the material. In the absence of information, a precautionary approach to labeling should be adopted. Specifically, warning signs indicating that radioactive nanomaterials are being handled should be posted at entrances to work areas. These signs should specify any requirements (*e.g.*, administrative and PPE) for entering the area.

Guidance on the types and use of access control systems that would be applicable to the use of radioactive nanomaterials is provided in NCRP Report No. 88, *Radiation Alarms and Access Control Systems* (NCRP, 1986).

5.2.2.6 *Selection of Engineered Controls*. Various factors influence the selection of appropriate containment and engineered controls for activities involving nanomaterials (radioactive or otherwise) including: material type (*i.e.*, physicochemical form), physical form (*e.g.*, bound, in suspension or aerosol), and task duration. For RNP, the activities of the radionuclides present and their decay characteristics (*e.g.*, half-lives and decay types, such as alpha particles, beta particles, gamma rays; and specific radionuclides which determine the applicable dose coefficients) will be important inputs to decisions on the most appropriate engineered controls.

Operations involving uncontained, easily dispersible nanomaterial powders deserve more attention and more stringent controls than those where the nanomaterials are embedded in a matrix or suspended in a liquid. NP in liquid suspensions rarely pose a significant danger of inhalation exposure during routine operations, but they may present a significant hazard when aerosolized or in unexpected situations such as a spill. If the spilled suspension subsequently dries, the dried material may be more available for dispersion. Activities such as ultrasonic agitation of nanomaterials in liquid suspensions can result in emission of NP-containing airborne droplets (NIOSH, 2013a). Dispersion of nanomaterials incorporated into bulk solids may pose some risk if the solid matrix is cut, sawed, drilled or handled in any way that creates a dust or releases the nanomaterial.

Logic flowcharts and tabulated guidance to assist in engineered control selection for nanomaterials (nonradioactive) are available from a number of sources (*e.g.*, HSE, 2013; NIOSH, 2012; UKNSPG, 2012). Detailed guidance on strategies for engineered controls for nanomaterial production and handling facilities is also available (NIOSH, 2013a). For radioactive nanomaterials, such guidance needs to be read in conjunction with general advice that systems containing radioactive materials in a dispersible form should have some degree of LEV and containment (NCRP, 1998) and more detailed guidance on appropriate engineered controls for radioactive sources based on activity levels and processes (*e.g.*, Homann and Aluzzi, 2014). Combining this guidance, the flowchart suggested in Figure 5.1 can be used for the selection of engineered controls for use with radioactive nanomaterials.

5.2.3 *Administrative Controls*

Administrative controls include safety procedures, job scheduling, and training. All employees working with radioactive nanomaterials should receive appropriate education and information on the potential health risks, both chemical and radiation, arising from exposure to such materials. Information, instruction and training should also be provided to ensure that the work practices and procedures in place, control measures provided, and any PPE required are used effectively to minimize potential exposures. Records of such training should be kept.

It is important that health physics and other occupational health personnel be involved in developing training that addresses both the separate requirements of radiation and nanomaterial safety and also reflects overlapping issues. There is a range of guidance available on the development and delivery of appropriate training for radiation safety (*e.g.*, NCRP, 2000) and general chemical safety (*e.g.*, OSHA, 1998) and also some guidance on safety training for working in nanotechnology (Kulinowski and Lippy, 2011a; 2011b; NIOSH, 2009; 2012; UKNPG, 2016). Specific guidance on suitable training for working with radioactive nanomaterials is, however, limited. It should be noted in this context that requirements for training on chemical and radiation hazards may be addressed by different regulatory agencies.

5.2.3.1 *Radiation Dose Control*. The objective of radiation dose control is to ensure that doses (from both external and internal exposure) to workers and members of the public are below recommended limits (*i.e.*, ICRP, 2007; NCRP, 1993) and follow the ALARA principle. These recommended limits are generally expressed as annual limits and are codified by various regulatory authorities.

In general, in addition to such overarching limits, organizations also develop dose guidelines (reference levels) that are set at a fraction of the occupational dose limits that are applicable to workers at particular sites, laboratories, and/or those performing particular operations and tasks. These are intended to ensure that doses are controlled to appropriate levels and are consistent with the radiation protection principle of ALARA.

In addition to individual specific dose guidelines, in many cases controls are imposed on specific work areas or activities on the basis of external dose rates and/or the likelihood of exposures to external radiation or contamination.

Clearly such controls are equally applicable in nanotechnology settings where radiation sources including radioactive nanomaterials are in use.

In all facilities where radiation sources (including RNP) are used, the building, facilities, processes, equipment, safety procedures, and planning activities should be designed and implemented to ensure that radiation doses are maintained within recommended limits and the ALARA principle. As discussed in the previous section, engineered controls should be the primary means for controlling doses. Administrative controls, such as safety procedures and training, also are a necessary part of any effective radiation safety program. Radiation monitoring and surveys also make an important contribution to radiation safety within the workplace. In addition to providing information on potential doses, they also allow an assessment of the efficacy of the engineered controls in place.

Typically dose controls for external doses and internal doses are addressed separately. Control procedures for external doses will be the same whether materials are nano-sized or otherwise, therefore standard operational health physics guidance will apply (*e.g.*, NCRP, 1998). The following sections are therefore focused on the control of internal radiation doses from radioactive nanomaterials and, in particular, how this may differ from that for larger particle sizes.

5.2.3.2 *Contamination Control*. It is important that formal policies and procedures be developed for both work areas and specific activities and tasks describing how work with radioactive nanomaterials is to be undertaken, including all actions taken to ensure the protection of workers. The procedures should incorporate guidelines for good work practices. Management should systematically review and update these procedures.

Health physics professionals often make use of simple software codes, flow charts, and tabulated “order of magnitude” estimates

when undertaking safety analyses of processes and facilities using radiation sources, or when giving advice on appropriate controls. For example, the HotSpot Program (Homann and Aluzzi, 2014), although intended primarily for emergency response purposes, includes a software tool for use in safety analyses of facilities handling radioactive material. Similarly, the tabulated radionuclide specific values in the *Radionuclide and Radiation Protection Handbook* (Delacroix *et al*., 2002) and similar references are widely used by health physics professionals.

Such tools and data resources provide guidance on the maximum activities of specific radionuclides that can be handled with the available equipment (*e.g*., standard chemical laboratory, fume hoods, gloveboxes). Delacroix *et al*. (2002), for example, provided data on maximum quantities of radionuclides suitable for use in low and intermediate level laboratories, although it is acknowledged that these are not applicable for high-level laboratories, where extensive professional radiation protection expertise would be available and appropriate control measures could be put in place. Such tools also make use of information on the operations involved (*e.g*., wet operations), the form of the material (*e.g*., solid, liquid, aerosol), the quantities of materials used, and the relative radiotoxicity of the materials to estimate such limit values. The relative radiotoxicity is generally expressed in terms of the dose coefficient for the particular radionuclide and its chemical composition, as generated primarily by ICRP (2012), or alternatively by a derived quantity such as the annual limit on intake (ALI) or derived air concentration (DAC), which are widely used in operational health physics. Derived quantities applicable to the inhalation exposure pathway (*e.g*., ALI_{inhal} and DAC) are determined assuming that the inhaled particles are micrometer sized.

In Section 6 it is concluded that, as a result of potential differences in the deposition, clearance, and biokinetic behavior of NP, standard dose coefficients, as produced by ICRP and NCRP models, may not be appropriate for RNP. If nanomaterial-specific dose coefficients are available they should be used in such systems. Also, it should be recognized that these practical operational radiation protection tools are typically based on simplistic and conservative assumptions (*e.g*., chemical form, dispersibility, containment factors) and are intended simply for broad categorization purposes. As such, it is considered that in general they will be broadly applicable to nanomaterials. However, all of these assumptions should be evaluated for appropriateness for use with RNP.

5.2.3.3 *Contamination Monitoring*. In any setting where radioactive materials are used, routine radiation surveys are important

tools to assess whether engineered controls are adequate and dose controls appropriate. The results from surveys are also potentially important inputs to exposure assessments, especially following accidental releases.

Guidance for operational health physics professionals on appropriate survey design and practice, including the choice of appropriate radiation monitoring equipment, is available from a number of sources, including NCRP Report No. 127 (NCRP, 1998). The majority of the available guidance is directly applicable to radioactive nanomaterials. The main additional factors to consider in relation to radioactive nanomaterials are:

- potential differences in internal radiation dosimetry (Section 6);
- potential requirements for additional measurement activities beyond those generally used, to determine or confirm particle characteristics (*e.g.*, NP aerosol size analysis requiring sophisticated equipment and specialized expertise) primarily in support of internal dosimetry calculations; and
- the increased potential for NP dispersion compared to larger particle sizes, particularly for samples in dry powder form.

The final factor should be considered in relation to survey design. It may be necessary, for example, to consider a wider area for surface contamination monitoring than for non-nano-sized materials. For example, Icenhour (2005) noted that when making decisions about containment strategies for radioactive materials, the special characteristics of the high-specific-activity alpha-emitting radionuclides must be considered. In particular, the fragmentation of these particles from alpha-induced radiation damage can increase the concentration of respirable particles with time. Additionally, the recoil of aggregates, combined with increasingly small aggregate sizes, can lead to resuspension and further airborne transport. Thus, alpha mobility is a factor to consider when determining where to set the boundaries for contamination control and monitoring.

It should be noted that monitoring of nonradioactive engineered nanomaterials in the work environment is complex with significant international research activities currently underway to develop appropriate instrumentation, techniques and protocols. The detectability of airborne ENP against background levels of many thousands of NP cm^{-3} in ambient air is a particular problem. By contrast, radioactive nanomaterials are generally significantly easier to detect than nonradioactive nanomaterials and monitoring for

radioactive materials is more straightforward compared to monitoring for nonradioactive materials. Use of radiation survey and sample counting equipment can generally be used to rapidly assess any potential exposure problems.

5.2.3.3.1 *Surveys for surface contamination of radioactive nanomaterials*. Routine surface contamination surveys are a standard approach used in environments where radioactive materials are used in solution or powder forms, to ensure control measures are adequate and doses controlled appropriately. Their use will be equally appropriate where the radioactive materials are nanosized. It is important, however, that survey design reflects the enhanced ability for NP, especially in dry powder form, to become airborne and deposit on surfaces some distance from the original source. Thus consideration when both planning and undertaking surface monitoring surveys may need to be given to investigating a wider potential area, including possible contamination of nearby walls and other proximal surfaces. Attention to accumulation of contamination on electrostatically charged surfaces such as computer screens in the workplace is warranted as charged surfaces have been shown to preferentially attract and collect ultrafine particles (Abdel-Naby and Ahmed Morsy, 2001).

If the RNP contain gamma and/or beta emitters, it may be possible to use direct reading contamination meters in low-background areas. In higher background areas, or if low-energy beta/gamma emitters or alpha emitters are used, wipe testing will be necessary. If a measurement of the total surface contamination (*i.e.*, removable plus fixed) is required, direct measurements will be necessary. Guidance for cleaning up spills and other surface contamination is provided in Section 5.6.

5.2.3.3.2 *Surveys for airborne radioactive NPs*. In facilities where radioactive aerosols are directly generated, or radioactive materials in potentially dispersible powder form are used or produced, for example, during processing or maintenance operations (*e.g.*, cleaning gloveboxes and chemical hoods or changing filters), airborne radioactive monitoring should generally be undertaken. Surveys for airborne radioactive materials are also frequently undertaken in situations where radioactive materials are used in solution in partially contained locations (*e.g.*, chemical laboratory hood), although this will depend on the amounts involved and the activities undertaken. Such requirements are applicable to all radioactive materials, including those nano-sized.

Surveys for airborne radioactive materials are typically undertaken by air sampling (*i.e.*, air is drawn through a filter which collects any activity in the air). The filter can then be counted using standard radioactive counting techniques and, by using the total volume of air sampled and a value for the collection efficiency, an airborne activity concentration (*e.g.*, Bq m^{-3}) can be determined. For the reasons discussed earlier it is expected that the capture efficiency of filters used will be high for NP, commensurate with or possibly higher than the capture efficiency of non-nano-scale radioactive aerosols. Typically such sampling will be undertaken using a sampler located at a static location (area sampling), but samples collected in the breathing zone may also be taken using personal air samplers.

Health physics guidance on radioactive air sampling (*e.g.*, Hoover, 2010a; 2011b; Maiello and Hoover, 2010a) is also applicable in circumstances involving radioactive nanomaterials, but note that the increased dispersion potential of nanomaterials may impact decisions on when to use and where to position samplers to obtain an appropriate picture of the spread of any contamination (Whicker, 2010). Guidance has been provided on approaches to correct for the presence of airborne radon decay products during air sampling for alpha-emitting radionuclides (Rodgers, 2010).

5.2.3.4 *Particle Characterization*. The physicochemical characteristics of a radioactive nanomaterial affect both its potential chemical toxicity (Section 4) and radiation dosimetry (Section 6). For a detailed discussion of the important physicochemical characteristics determining the chemical toxicity of any nanomaterial, refer to NIOSH (2009; 2012). In relation to radiation dosimetry, NP size plays a key role in determining the efficiency of particle deposition within the lung and may also influence clearance mechanisms within the respiratory tract. Therefore in any setting where radioactive nanomaterials are used, the details of the physicochemical characteristics of the materials to which people may be exposed (*i.e.*, properties of the original material, properties of the material after any processing, or properties of the portion of the material that may be dispersed as the result of foreseeable release scenarios) are important input to hazard and risk assessments.

5.2.3.4.1 *Airborne NPs*. The chemical composition of the material and the particle size distribution are the key inputs to radiation dosimetry for inhaled radioactive particles. Guidance on appropriate instrumentation and measurement strategies for airborne NP is available from a number of sources (Eastlake *et al.*, 2016;

NIOSH, 2009; 2012; 2013a; UKNPG, 2016). Measurement of aerosol particle size is a specialist operation, with most instrumentation expensive to purchase and complex to use. It is recommended that advice be sought from experts in this area prior to undertaking such activities. The reader is referred to Hinds (1999), Kulkarni *et al*. (2011a), and Maiello and Hoover (2010a) for background on the measurement of airborne particles.

Instruments and methods for measuring particle size distributions for airborne NP involve a number of measurement principles and include:

- *Condensation particle counters*: enable real-time measurement of PNC in a specified size range such as 1 to 1,000 nm (Figure 5.3).
- *Optical particle counters*: enable real-time analysis of PNCs within a specific size range such as 300 nm to 10 μm (Figure 5.3).
- *Scanning Mobility Particle Sizers*® [SMPS® (TSI, Inc., Shoreview, Minnesota)]: enable online real-time analysis of particle electrical mobility size distributions with good resolution (Figure 5.4). SMPS® generally comprise a differential mobility analyzer, which selects the aerosol within a certain size range, coupled to a condensation particle counter (next bullet), which counts the number of particles within that size range. By scanning across the complete size range, a full particle mobility size distribution is acquired.
- *Cascade impactors, including the Electrical Low Pressure Impactor*® [ELPI® (Dekati Ltd., Kangasala, Finland)] and the nano Multiple Orifice Uniform Deposit Impactor [nano-MOUDI® (MSP Corporation, Shoreview, Minnesota)]: allow size fractionation of airborne particulates by inertial impaction into a number of size bands (Figure 5.5). Some instruments allow collection of size fractions onto filters for post-sampling gravimetric and imaging analysis.
- *Electron microscopy*: after sampling from the aerosol using "filters" or electrostatic precipitators, this technique provides an offline analysis of samples that can give information on shapes and sizes as well as, by using appropriate counting techniques, number concentrations.

For measurements using the ELPI®, particles are first electrostatically charged to a known level as shown in the schematic diagram of operation in Figure 5.5. After charging, they enter a cascade impactor and are collected in the different stages depending on their aerodynamic diameter. The electrical charge carried by

Fig. 5.3. Example instruments for measuring the airborne concentration of NPs include (left) the Condensation Particle Counter (TSI Model 3007) and (right) the Optical Particle Sizer (TSI Model 3330) [courtesy of TSI (2012)].

Fig. 5.4. An example instrument for measuring the electrical mobility particle size distribution of airborne NPs is the Electrical Mobility Particle Sizer® (TSI 3938 SMPS® Spectrometer) [courtesy of TSI (2010)].

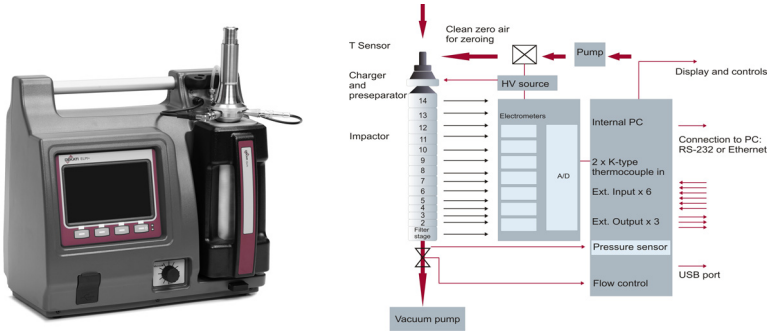


Fig. 5.5. An example instrument for measuring the aerodynamic particle size distribution of airborne NPs is the ELPI® [courtesy of Dekati (2015)].

particles in each impactor stage is measured by electrometers and the current is proportional to PNC and size. Note that the use of high-velocity impaction jets to apply high-inertial forces to very small particles in devices such as the ELPI® and nanoMOUDI® does not mimic normal environmental conditions and that the resulting measurements of particle size require expert interpretation for assessment of situations such as dispersion in the workplace or inhalation and deposition in the respiratory tract. Appendix C.4 discusses the relationships among aerodynamic diameter, thermodynamic diameter, electrical mobility diameter, geometric diameter, and their relevance for assessing particle behavior.

As indicated earlier, one of the difficulties in characterizing NP aerosols, and thus exposure, in nanotechnology settings is the need to identify the ENP in the aerosol against the background of ambient nano-sized particles, which can arise from a number of natural or incidental sources. The confounding influence of ambient background aerosols is generally addressed by detailed surveys before and after the introduction of the nanomaterial or process. It is important to recognize however that if detailed characterization is undertaken at the initial stage of an operation then only limited confirmatory particle characterization activities may be required on an ongoing basis, and reliance can be placed on the initial assessments (*e.g.*, of size) combined with the use of radiation survey techniques. In those cases where surveys of airborne contamination reveal very low airborne concentrations, then detailed size characterization may not be necessary.

When characterizing RNP, the collection and analysis process can be somewhat simplified. For example, a nanoMOUDI® can be used to size-segregate the aerosol within various size ranges, and the aerosol within each size range can be captured on a filter and radioactive counting techniques used to determine the concentration of RNP within that size range. An alternative option is to use a differential mobility analyzer to select airborne particles within a size range and to capture these onto a filter, again for radioactivity counting.

A unique difficulty in characterizing RNP aerosols of alpha-emitting materials is the challenge of differentiating the naturally occurring alpha-emitting decay products of radon and thoron from other alpha-emitting radionuclides such as plutonium. As noted by Rodgers (2010) some alpha continuous air monitors include a virtual impactor at the aerosol inlet to divert airborne NP or use a porous screen at the aerosol inlet to remove airborne NP by diffusion. These methods to avoid collecting radon decay products may not be suitable for use when NP of a material such as plutonium needs to be measured.

5.2.3.4.2 *NPs in liquid suspensions and bulk powders*. In general it is anticipated that size characterization of RNP in liquid suspensions or powders will only be necessary in instances of inadvertent intake. Choosing appropriate instrumentation, techniques and protocols for such studies is a specialist task for which expert advice should be sought. For an evaluation of the available techniques, the reader is referred to Linsinger *et al*. (2012).

5.2.4 *Personal Protective Equipment*

In the working environment, reliance for safety should be placed primarily on engineered controls rather than on PPE and administrative controls. However, there may be situations that require the use of individual respiratory protective equipment (RPE), for example, following unplanned releases of radioactive material or "dirty" operations such as infrequent cleaning or maintenance operations, particularly with contaminated gloveboxes. Protective clothing is generally required in working environments using radioactive materials to prevent contamination of workers' skin and personal clothing, and thus to minimize external doses and potential inadvertent intakes of radioactive material, and to reduce the potential for contamination spread. The selection of PPE should be based on an appropriate risk assessment, including hazard and exposure evaluations, which results in a clear indication of the level of protection that is required. AIHA (2015b) has developed a fact sheet on PPE for engineered nanomaterials.

Existing guidance on the use of PPE (including protective clothing and respiratory protection) for work with radioactive materials in general will be valid for radioactive nanomaterials. The main potential issues when using radioactive nanomaterials relate to the possibility of greater penetration through clothing and, because of the mobility of NP in air, potential performance issues regarding respiratory protection (Section 5.2.4.2).

5.2.4.1 *Protective Clothing*. In the context of operational radiation protection, protective clothing is used to avoid getting contamination on workers and to prevent the spread of contamination. In some cases it is also used to provide radiation shielding against sources of external radiation. Protective clothing for external radiation includes lead impregnated gloves and aprons. Available guidance on the selection of such clothing (*e.g*., NCRP, 1989b) is equally applicable whether the radioactive materials are nano-sized or otherwise. When removing protective clothing, care should be taken to avoid resuspending and inhaling NP from contaminated clothing.

5.2.4.1.1 *Eye protection*. When handling any dispersible materials, safety goggles should be used at a minimum (NIOSH, 2012). If high concentrations of airborne nanomaterials could be encountered, full-face respiratory protection might be more suitable.

5.2.4.1.2 *Gloves*. Chemically impervious gloves manufactured to an appropriate standard should be selected (*e.g.*, ANSI/ISEA, 2011). The proper selection of gloves ideally should take into account the permeability of the glove to the nanomaterial (if this is known) and, if the nanomaterial is suspended in a liquid, the characteristics of the liquid. Unfortunately there is currently little information on the permeability of NP through gloves. As part of the European NanoSafe Project (NanoSafe, 2014) limited studies of NP diffusion through gloves were undertaken (Golanski *et al*., 2008), which demonstrated penetration that varied with glove material and thickness.

In preliminary studies Dolez *et al*. (2013) found limited permeability of glove materials to NP with no penetration of dry particulate NP through typical glovebox glove material (butyl). For use with many particulate radioactive nanomaterials, good quality disposable, single-use gloves should be adequate. However, under some circumstances consideration may need to be given to wearing two layers of disposable gloves, and this should be standard practice if using high aspect ratio radioactive nanomaterials (*e.g.*, radioactive CNT or other nano-fibers). Using two layers of gloves reduces the potential penetration of NP and can also improve contamination control. As with all gloves, special attention should be given to ensuring appropriate overlap of gloves with other protective clothing. Routine replacement and proper removal practices should be used to minimize the risk of contamination and exposure. Employees should be properly trained in how to put on and remove gloves without contaminating themselves and their working environment and to wash hands after wearing gloves. Contaminated gloves should be kept in a plastic bag or other sealed receptacle until disposal.

5.2.4.1.3 *Other clothing*. In general, clothing appropriate for a laboratory should be worn, with full leg and arm cover and suitable laboratory coats or overalls. This would also include closed-toe shoes (note that disposable "overshoes" may also be necessary to minimize contamination spread). If reusable coats are used, they should remain in the laboratory between use to minimize potential contamination spread to other areas. Provision should also be made to allow clean overalls/lab coats to be put on and dirty ones removed

in a manner that does not contaminate the individuals or the workplace. Regular laundering of reusable lab coats should be undertaken in such a way as to minimize secondary exposure.

In general, reusable clothing manufactured from woven materials (*e.g.*, cotton mixes) will be suitable. However, if there could be significant potential exposure to radioactive nanomaterials, in particular in dry forms, then consideration may need to be given to the choice of more specialized clothing with limited NP permeability and to the use of disposable clothing. In such circumstances clothing made from low-dust release fabrics such as polyethylene textiles is recommended. The European NanoSafe Project reported in 2008 that particulate nanomaterials can permeate through some intact disposable overall materials, and by implication, woven reusable materials. They have therefore recommended nonwoven Tyvek®/Tychem® (E.I. du Pont de Nemours and Company, Wilmington, Delaware) polyethylene overalls for use with particulate nanomaterials in preference to paper or cotton overalls (Golanski *et al*., 2008). In addition, the use of duct tape over zippers on protective clothing may help minimize the penetration of NP through this route.

An advantage of the use of radioactive nanomaterials is that contamination on clothing including shoes can be easily detected using standard radiation monitoring procedures and thus efforts to minimize the spread of contamination from "active" laboratories to other areas can be monitored for effectiveness. Procedures should be put in place, including appropriate barrier controls, to ensure that such monitoring is undertaken.

5.2.4.2 *Respiratory Protection*. There will be situations where other control measures are either not practicable (*e.g.*, removing potentially contaminated glovebox windows) or fail to achieve adequate control. In these circumstances, and also as a response to accidents and incidents, the use of RPE is a valid control strategy. RPE should not, however, be generally used as the primary exposure control technique. Available guidance on the use of RPE to control exposures to airborne radioactive materials (*e.g.*, NCRP, 1998) will generally be valid for radioactive nanomaterials. All RPE should be suitable for the task, manufactured to the appropriate standard, and face-fit tested for the individual.

Judgment is clearly required in determining the need for and type of respiratory protection because use may impede the worker's ability to undertake tasks and thus potentially increase exposure to the hazard. Guidance on the choice of RPE is provided in *NIOSH Respirator Selection Logic* (Bollinger, 2004). Information on the science and rationale behind the NIOSH recommendations for the use

and selection of respirators against ENP, as well as an opportunity for interested individuals to share comments and questions is available in the *NIOSH Science Blog* on respiratory protection for workers handling ENP (Zhuang and Viscusi, 2011).

5.2.4.2.1 *Effectiveness of RPE*. Various studies have generally shown that currently available RPE are efficient filters of NP and they meet the minimum percentage filtration efficiency required for each filter type. These studies are summarized below.

Shaffer and Rengasamy (2009) undertook a review of studies investigating respiratory protection against NP. They found high filtration efficiencies for NP from 4 to 20 nm and the MPPS range for electret filter media (the most common type of filter used in respirators on the market today) was between 30 and 100 nm. This lower MPPS compared to other fabric filters (*e.g.*, system exhaust filters discussed in Section 5.2.3.3) is a result of the significant impact of electrostatic capture mechanisms for electret filters, which maintain an electric charge during use.

Rengasamy *et al*. (2008) investigated penetration efficiencies for NIOSH approved N95 and P100 filtering face-piece respirators (FFRs) using particles ranging in size from 4 to 20 nm. The data from this study confirmed that NIOSH-approved N95 FFRs and P100 FFRs provide filtration performance of >95 and 99.97 %, respectively, against such particles. Consistent with single-fiber filtration theory for the collection of airborne particles, their work demonstrated an increase in the filtration efficiency for N95 and P100 FFRs as particle size decreased below 30 nm. They found that MPPS values for the N95 and P100 FFRs in this study were in the 40 to 50 nm range.

In a study of eight different models of NIOSH-approved FFRs and elastomeric half-face respirators, Vo *et al*. (2016) found the penetration of SWCNTs and MWCNTs to be 0.18 to 1.09 % for the N95 class respirators and 0.004 to 0.019 % for P100 class respirators. Those respirator performance results are better than the acceptable penetrations of 5 % for the N95 class and 0.03 % for P100 class. The CNT aerosols were representative of dispersion of CNTs during workplace handling of CNT powders.

Rengasamy *et al*. (2009) undertook a comparison of the filter performance of NIOSH approved and "CE marked" (*i.e.*, meeting the requirements of European Union safety, health and environmental legislation) filtering respirators, which indicated that the respirators provided expected levels of filtration performance (Figure 5.6). Eshbaugh *et al*. (2009) also investigated penetration efficiencies for N95 and P100 respirators using particles ranging in

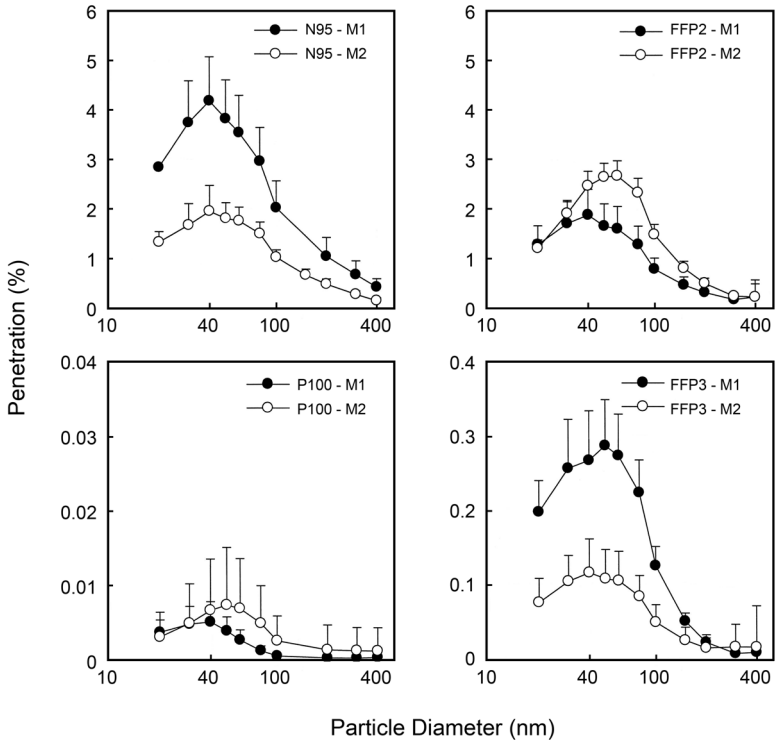


Fig. 5.6. Percentage penetrations of monodisperse particles through N95, FFP2, P100, and FFP3 filtering face-piece respirators from two manufacturers (M1 and M2) (error bars represent the 95 % confidence interval, n = 5). Note that the required minimum percentage filtration efficiencies are 95, 99.97, 94, and 99 for respirator types N95, P100, FFP2, and FPP3, respectively (Rengasamy *et al*., 2009).

size from 20 nm to 2.9 μm. The MPPS was between 50 and 200 nm for the P100 and was ~50 nm for the N95, which is broadly consistent with the results from Rengasamy *et al*. (2008; 2009). As noted by Rengasamy *et al*. (2013), the MPPS is ~40 nm for electrostatic filters and ≥150 nm for mechanical filters. Plebani *et al*. (2012) also investigated the efficiency of respirator filters using aerosols in the range 30 to 400 nm and, consistent with Rengasamy *et al*. (2009), found an MPPS of 50 nm at the start of the study.

Rengasamy *et al*. (2009) also studied the effect of buildup of material on the filters, which reduced the overall filtration efficiency. This finding illustrates the importance of regular filter changing. Plebani *et al*. (2012) also found that treating the filter with isopropanol to reduce the electrostatic capture efficiency caused the MPPS to increase to ~300 nm.

5.2.4.2.2 *Prevention of respirator face-seal leakage*. An important underlying concept for respiratory protection is the assigned protection factor (APF), which is defined as the minimum anticipated protection provided by a properly functioning respirator or class of respirators to a given percentage of properly fitted and trained users (OSHA, 2006). Consistent with this definition, a respirator with an APF of 10 would be acceptable for use in work conditions where the airborne concentration of an aerosol of concern is not more than 10 times the allowable concentration.

Face-seal leakage is the primary reason that the APF for a given type of respiratory protection is lower than the value that would be based on filtration efficiency alone. For example, as noted by Rengasamy *et al*. (2008) the APF of 10 for N95 and P100 FFRs suggests that up to 10 % of airborne particles, including those in the 4 to 30 nm range, could still penetrate the face seal even after properly sized, fitted and worn in a workplace and this fact should be taken into account when selecting a respirator for protection against NP. Thus, although the studies noted above show that current RPE meet the minimum specified filtration efficiencies for the various filter types and are therefore generally suitable for working with NP, the successful use of RPE for protection against airborne particles of any size requires both effective individual face-fit testing of devices and also appropriate checking and maintenance of such equipment.

In a study to assess whether NP preferentially leak past the face seal of respirators compared to larger particles, Rengasamy and Eimer (2011; 2012) put respirators on a manikin and created various size-controlled leaks in the respirator face seal. They found for particles of all sizes that leak size was the largest factor affecting the number of particles inside the face piece of the respirator worn on the manikin, although for small leaks, NP were more likely than larger particles to be found inside the face piece of disposable N95 FFRs. Similarly, Mouret *et al*. (2009) found that for fibrous filters perforated with defined pinholes, penetration increased as particle size decreased.

Brochot *et al*. (2012) undertook a study of the effectiveness of RPE against NP and found in tests with two types of half-masks that when leaks (face piece/manikin face) were negligible, the efficiency of the equipment provided a great deal of protection. For major leaks, the protection factor was found to decrease independently of the particle size (*i.e*., major leaks enable particles of all sizes to freely bypass the face seal).

The document *NIOSH Respirator Selection Logic* (Bollinger, 2004) provides general guidance on respirator selection. Additional

guidance is available from NIOSH (2009) on the choice of respirators for nanotechnology settings, including Table 8-1 that provides estimates of NP filtration efficiencies for various RPE. In all cases, employees should be properly trained in RPE use and supervised. If the equipment is reusable, it should be regularly cleaned and checked to ensure it remains effective.

5.3 Use of Radioactive Nanomaterials in Medical Settings

The analysis of potential uses of RNP in Section 3 indicated that the medical field is the major area of current interest in nanotechnology, with applications in both diagnosis (particularly imaging) and treatment of disease being explored. For this reason it is appropriate to consider the implications for operational health physics of the use of nanomaterials in the hospital sector in more detail. As also indicated earlier in Section 3, it is clear that current guidance for the medical area (ICRP, 2007; 2013; NCRP, 2010a) will be generally applicable when RNP are being used, with only minor modification. However, when designing and developing new treatments and imaging agents using RNP, consideration will need to be given to potential differences in their behavior within the body in comparison with radioactive chemical compounds or larger radioactive particles (Section 6).

It is anticipated that the absolute quantities, in activity terms, of RNP used in novel radiopharmaceuticals would not be significantly different from those in conventional radiopharmaceuticals, as the overall objectives of the treatment (*e.g.*, imaging or tumor irradiation) would require similar activity levels. In fact it is hoped that the properties of NP may mean that lower activities could be used in some instances.

In general RNP in the medical arena would be found suspended in liquid for patient delivery. As described in Appendix A.6, nonradioactive NP in liquid suspensions are also being used in conjunction with radiotherapy to enhance the radiation dose or thermal effects to tumors (Berbeco *et al.*, 2016; Martinez-Rovira and Prezado, 2015; Ngwa *et al.*, 2012; Paudel *et al.*, 2016; Sinha *et al.*, 2015). In such cases standard operational health physics and industrial hygiene practices would apply unless there was the potential for aerosols to be formed (Figure 5.1). Clearly the area of most concern for RNP is when they are in aerosol form with the increased potential for inhalation by workers.

There is a history of the use of radioactive aerosols for the assessment of pulmonary and cardiac function, and such procedures require careful control. One such aerosol, technegas, comprises RNP (^{99m}Tc-labeled carbon NP; see Section 3 and Appendix A

for a detailed description) and experience with health physics controls for its safe use could be useful in relation to other potential applications of RNP in aerosol form (Lloyd *et al*., 1994; Lopez Medina *et al*., 1999; Smart, 2004).

5.4 Management and Disposal of Radioactive Nanomaterial Waste

Radioactive nanomaterial waste can be broadly classified into the following waste streams:

- pure radioactive nanomaterials;
- items contaminated with radioactive nanomaterials (*e.g*., gloves, other PPE, paper towels, wipes, HEPA filters);
- liquid suspensions containing radioactive nanomaterials;
- solid matrices with radioactive nanomaterials that are friable or attached to the surface; and
- radioactive nanomaterials embedded in a matrix so that they are unlikely to be released on contact with air or water (*i.e*., immobilized).

The management and disposal of radioactive and chemical wastes is an area in which regulatory requirements play a key role. Typically, radioactive and chemical wastes are addressed by separate regulatory regimes. It is therefore important to consider the full range of applicable regulatory requirements when determining appropriate waste management approaches to radioactive nanomaterials. In essence, the approach taken should consider the requirements, regulatory and otherwise (*e.g*., local and national programs for reuse, recycling, and waste minimization), that apply to all aspects of the material (*i.e*., chemical, nano-scale and radioactive).

There is some guidance available on management of nanomaterial waste (HSE, 2013; NIOSH, 2009; 2012; UKNPG, 2016). The nanomaterial-specific guidance (*e.g*., to double bag laboratory consumables, such as paper towels, wipes, gloves, and suits in preparation for disposal) would be equally valid for radioactive nanomaterials. There is a range of guidance on the appropriate handling and disposal of both radioactive wastes (*e.g*., NA/NRC, 2011; NCRP, 2003) and chemical wastes (*e.g*., NA/NRC, 2011). The U.S. Environmental Protection Agency (EPA) has also issued regulatory requirements for the disposal of chemical wastes (EPA, 2001). Although the DOE has also issued general regulatory requirements for the disposal of nonradioactive nanomaterial wastes (DOE, 2011), there currently is no guidance directly targeted at disposal of radioactive nanomaterials.

When considering the acceptability of releases of radioactive materials (and chemicals in general) to the atmospheric and aquatic biospheres, factors such as the scope for dilution and potential reconcentration within the environment (*e.g.*, concentration within certain plant species or on soil minerals) need to be considered. Although a detailed discussion of the fate of radioactive nanomaterials released to the environment is beyond the scope of this Report, it should be noted that nano-sized materials may behave differently from larger particles with different dissolution, concentration, and uptake patterns (Batley *et al.*, 2013; Klaine *et al.*, 2008; Rosenkrantz *et al.*, 2009).

5.5 Control of Public Exposure

NCRP has recommended dose limits for exposure of members of the public to sources of ionizing radiation (NCRP, 1993). Specific dose limits for members of the public are specified by regulatory agencies. These regulatory requirements apply equally whether the radiation sources are nano-sized or otherwise. It is important that facilities are operated within such dose limits, but clearly the primary requirement is to ensure that public exposures adhere to the ALARA principle. These objectives are achieved by controlling external radiation fields and radioactive releases from the facility into the environment. General guidance on the control of exposures to members of the public is provided in NCRP Report No. 127 (NCRP, 1998).

Addressing controls clearly begins at the design stage, and the facility operators should ensure that the control measures are appropriate and functioning correctly. Demonstrating satisfactory operation typically includes monitoring activities within the facility and in some cases environmental monitoring beyond the site. Also, because naturally occurring nanomaterials (and possibly incidentally produced radioactive nanomaterials, depending on the facility) are ubiquitous in the environment (Section 3.4), it may be useful to perform environmental monitoring before operations begin. This preoperational monitoring of background levels of radioactive nanomaterials can then serve as a basis for comparison after operations begin.

Clearly the application of good administrative controls requires that such activities are suitably planned and that records are kept. Guidance on radioactive effluent monitoring and environmental surveillance is provided in NCRP Report No. 169 (NCRP, 2010b). In some circumstances it may be necessary to undertake assessments of the doses received by members of the public from facility operations. For facilities handling small quantities of materials, screening assessments [*e.g.*, as provided in NCRP Report No. 123 (NCRP, 1996)] may be appropriate.

The choice of control measures is dependent on a number of factors, including the quantities and types of radionuclides and radiation sources present and the processes undertaken. As a demonstration of methods to determine the need for workplace controls of ENP, Casuccio *et al*. (2009a; 2009b; 2010) conducted a series of worker and environmental assessments of the releases of unbound ENP during actual laboratory research. They used a combination of airborne particle counting and electron microscopic examination of collected particles to estimate airborne ENP releases from activities such as the processing and handling of nanosilicon and carbon black. They assessed the potential dispersion of the airborne material to locations off-site from the laboratory site using the EPIcode Gaussian Plume Model (DOE, 2004b).

Activities undertaken to demonstrate systems are functioning correctly (*e.g*., workplace monitoring, stack monitoring, and environmental surveillance) will also depend on similar factors, including the quantities of radioactive materials that could be released.

Potential exposures of members of the public to external radiation fields from sources within a facility are controlled by appropriate shielding and standard guidance will be equally applicable in nanotechnology settings. Airborne and liquid effluents are controlled by waste-stream treatment processes including filtration. As indicated previously (Section 5.2.2.3), filters for radioactive airborne particulates are expected to be suitable for the control of RNP aerosols. Clearly simple liquid radioactive waste management approaches, such as decay-in-storage, will be equally effective for nanomaterials. However, the behavior of NP in complex liquid radioactive waste treatment plants has not been studied.

Currently engineered RNP are typically being produced in small volumes in laboratory scale processes. Such processes are generally undertaken in laboratory chemical hoods, gloveboxes, or other containment with HEPA filtration. Airborne releases to the environment from such systems are expected to be minimal and monitoring external to the site should not be required.

Liquid wastes from RNP production processes will also likely be small in volume and typically either immobilized to produce materials for disposal *via* solid waste disposal streams or released to drains under appropriate controls. It is not expected that such operations would require the implementation of environmental monitoring procedures or the assessment of doses beyond simple screening approaches (NCRP, 1996). For any future large-scale production of RNP, the effectiveness of effluent treatment practices for controlling radionuclide releases to the environment and potential exposures to members of the public will need to be evaluated.

5.6 Emergency Response

RNP currently are only produced in small amounts and the expected specialized applications of such materials mean that it is unlikely in the foreseeable future that significant bulk quantities will be produced at any single site. The possibility of significant material releases with the potential for widespread contamination involving many people is, therefore, currently negligible. The main focus of emergency planning and response thus relates to potential accidental exposures arising from spills or leaks. The possibility of such incidents occurring will clearly be minimized by appropriate applications of the principles of control outlined earlier. However, it cannot be eliminated, especially for the small-scale research environments in which such materials are typically used. Therefore, appropriate plans should be put in place to deal with such events. In particular, procedures for dealing with spills and leaks of RNP should be developed and workers given appropriate training.

After a spillage or leak of any radioactive material, a key objective of the cleanup operation is to minimize potential exposures, both for those involved and any others who could potentially be affected. This requires the institution of appropriate area controls and equipment, PPE, and monitoring. Guidance for operational health physics and associated professionals on developing and applying plans for dealing with radioactive incidents is available from a number of sources, including NCRP Report No. 127 (NCRP, 1998). This existing guidance will be applicable to RNP. However, in developing plans for dealing with incidents involving such materials, additional consideration may need to be given to the enhanced potential for NP to be dispersed and to remain airborne in comparison to larger particles.

Guidance on dealing with nanomaterial spills (HSE, 2013; NIOSH, 2009; 2012; UKNPG, 2016) recommends that, to limit the potential for inhalation exposures, the preferred approach is to clean the affected area by wet wiping. Any cleaning liquids used (*e.g.*, mild soap and water or other cleaning solutions or oils) should be compatible with the spilled material and the affected surfaces. To avoid resuspension of the spilled material, cleaning liquids should not be directly sprayed onto affected surfaces, but rather should be applied to the disposable wipes or sorbent materials before use. It is considered inappropriate to sweep, brush or use compressed air for cleaning under these circumstances as it may result in resuspension of the material. If the only practicable approach to cleaning is the use of a vacuum cleaner, then it should be a dedicated HEPA-filtered cleaner and the filter should be regularly checked for efficiency under controlled conditions. Liquid spills

can typically be cleaned by applying disposable absorbent materials. In some settings, the provision of "spill kits" may be appropriate. The contents will depend upon the circumstances but could include (NIOSH, 2012):

- barricade tape;
- warning signs and labels;
- gloves;
- RPE;
- wipes;
- absorbent material;
- an appropriate cleaning liquid;
- sealable plastic bags; and
- step-off pad for contamination control.

Appropriate contamination monitoring (Section 5.2.3.3) will allow effective cleanup actions to be evaluated and, if required, provide input to exposure estimates.

The treatment and disposal of any wastes produced should follow the guidance in this section including any applicable regulatory requirements.

In general, an investigation of any significant radiological incident involving radioactive materials will be required. Summary guidance on performing radiological incident investigations is provided in Section 5.7.

5.7 Incident Investigation

Guidance on the investigation of radiological incidents is provided in NCRP Report No. 173 (NCRP, 2012). That guidance can be applied to radiological incidents involving nanotechnology. NCRP (2012) also provides guidance on when an incident investigation might be required and how to tailor the extent and rigor of the investigation to the severity of the incident. A brief summary of the steps in the investigation process is:

- respond to the incident;
- coordinate the incident recovery process;
- conduct the incident investigation including using cause analysis techniques;
- determine the consequences;
- develop a corrective action plan;
- prepare the investigation report;
- schedule follow-up actions; and
- review the effectiveness of corrective actions.

Regarding the final point, as noted by NCRP (2012), the review of the effectiveness of the cause analysis investigations should be part of a self assessment as discussed in NCRP Report No. 162 on *Self Assessment of Radiation-Safety Programs* (NCRP, 2009c).

5.8 Effective Risk Communication

Operational health physicists are often called on to provide or to communicate information about risks associated with handling radioactive materials, especially after incidents occur. In the case of radioactive nanomaterials, most of the potential risks to workers and members of the public associated with their use will be similar to those for non-nano radioactive materials. The primary additional potential risk factors that should be addressed for radioactive nanomaterials are their potential physiochemical toxicity, their potential differences in deposition and transfer within the body and their elimination from the body, and their potentially increased mobility in the workplace and the environment.

A useful presentation of approaches to effective public information and risk communication is provided in NCRP Report No. 175 on *Decision Making for Late-Phase Recovery from Major Nuclear or Radiological Incidents* (NCRP, 2014). Although, this report deals with large nuclear incidents that have a major impact on members of the public, the basic principles would be applicable to communicating with workers or members of the public following minor incidents. As noted by Johnson (2011), it is prudent to be prepared to address the psychological and mental health aspects of exposure to ionizing radiation before, as well as after, those exposures occur.

As noted by NCRP (2014), the following seven cardinal rules for effective risk communication described by Covello and Allen (1988) are the foundation for effective risk communication:

- *People have the right to have a voice and participate in decisions that affect their lives*.
- *Plan and tailor risk communication strategies*: Different goals, audiences, and communication channels require different risk communication strategies.
- *Listen to your audience*: People's perceptions of risk are influenced by factors other than numerical data. People are usually more concerned about psychological factors, such as trust, credibility, control, voluntariness, dread, familiarity, uncertainty, ethics, responsiveness, fairness, caring and compassion, than about the technical details of a risk. To identify public concerns about risk, organizations should be willing to listen carefully to and understand the audience.

- *Be honest and transparent*: Honesty and transparency are critical for establishing trust and credibility. Trust and credibility are among the most valuable assets of a risk communicator. Once lost, it is extremely difficult to regain.
- *Coordinate and collaborate with credible sources of information and trusted voices*: Communications about risks are enhanced when accompanied by validation by sources of information perceived to be credible, neutral and independent. Few things hurt credibility more than conflicts and disagreements among information sources.
- *Plan for media influence*: The media plays a major role in transmitting risk information. It is critical to know what messages the media are delivering and how to deliver risk messages effectively through the media.
- *Speak clearly and with compassion*: Technical language and jargon are major barriers to effective risk communication. Abstract and unfeeling language often offends and confuses people. Acknowledging emotions, such as fear, anger and helplessness, is typically far more effective.

Kahan (2009) noted that public perceptions of the risks of nanotechnology are evolving. Kahan and Rejeski (2009) presented a comprehensive strategy for nanotechnology risk communication, which involves aspects of message framing, credibility, and the recognition that the best scientific evidence will not necessarily nor automatically permeate public opinion and policy making. Kahan *et al*. (2009) have found that how people react to information depends largely on their values and further have determined that how individuals interpret information on nanotechnology risks varies depending on whether the emphasized application of nanotechnology affirms or threatens their cultural values.

Hoover *et al*. (2014; 2015) recommended steps for clear communication and the application of an informatics-based decision making framework and process to the assessment, communication and management of risk at the convergence of nanotechnology and radiation-related activities. An informatics goal is to identify and assemble a useable body of knowledge from authoritative sources and to make that information available to the radiation protection community.

6. Nanoparticle Issues for Internal Radiation Dosimetry

6.1 Framework for Considering Radioactive Nanoparticle Internal Dosimetry

Radioactive nanoparticle (RNP) intakes will result in spatial and temporal radiation dose distributions for the various tissues and organs of the body that depend on the characteristics and biokinetics of the NP. In particular, the radiation dose patterns will be influenced by the decay properties of the radionuclide (*i.e.*, types of radiation emitted, physical half-life) as well as the physicochemical properties of the RNP (*e.g.*, chemical form and solubility, particle size and shape, mass and number, route of exposure) and subject characteristics, such as age, gender, size, and state of health. In some cases, the spatial distribution of dose can be relatively uniform (*e.g.*, with exposure to relatively soluble forms of ^{137}Cs NP), but in most cases the dose distributions will be heterogeneous with respect to the whole body. Additionally for radionuclides that decay with short-range emissions such as alpha particles or low-energy beta particles, microdosimetric considerations for local dose distribution may be affected by the small size of RNP and the ability to attach radioactive atoms to monoclonal antibodies for radioimmunotherapy to treat cancer while limiting radiation to healthy tissues (*e.g.*, Bouchat *et al.*, 2010). Note, however, that the attenuation of short-range emissions such as alpha radiation in NP is not significantly less than in micrometer-sized particles, so the doses from emissions originating in nano-sized particles are not expected to be significantly greater than the doses from emissions originating in micrometer-sized particles. For example, according to Berger *et al.* (2005) the range of an alpha emission from ^{238}Pu or ^{239}Pu is ~10 μm in a PuO_2 particle of density 10 g cm^{-3} and ~40 μm in tissue. Thus, for a PuO_2 particle with the ICRP default occupational exposure particle size of 5 μm AMAD and a corresponding physical diameter of ~1.7 μm for material of density 10 g cm^{-3}, even those alpha emissions traversing the entire particle diameter from edge

to edge would have only a fraction of their energy absorbed in the particle.

Because of the known differences in radiosensitivity of various target tissues, taken together with the large range of dose heterogeneity that can occur, ICRP has developed and implemented a dosimetry system that takes these factors into account through the use of quantities that link physical dose (*i.e.*, absorbed dose) with risk, using equivalent dose, and effective dose (ICRP, 2007). This dosimetry system, which was designed for developing radiation protection programs for both workers and members of the public, also can be considered by default to apply to RNP. In this section, the unique physical, chemical and biological properties of RNP will be compared with the dosimetric assumptions and features of the current models published by ICRP and NCRP as applied to intakes *via* inhalation (ICRP, 1994a), ingestion (ICRP, 2006a), or wounds (NCRP, 2006). The intent is to assess the adequacy of the existing dosimetric models for dealing with RNP in a radiation protection context.

An additional but important consideration in examining the appropriateness of dosimetry and dosimetry modeling for RNP relates to the biological behavior of RNP *in vivo* that are not associated with their radiological characteristics (*i.e.*, their chemical and particulate properties). These biological effects have been studied for several decades, and have shown that nonradioactive NP, particularly if inhaled, can access inter- and intracellular spaces not commonly encountered with larger sized respirable particles (*i.e.*, >0.1 μm), and, at very high doses, can result in inflammatory and fibrotic lung injury in rats as well as lung cancer, which is similar to findings of inhaled micro-particles in lung overload conditions (Borm *et al.*, 2006; Donaldson, 2006; Geiser, 2010; Heinrich *et al.*, 1995; Johnston *et al.*, 2013; Kreyling *et al.*, 2013; Oberdorster, 2010; Oberdorster *et al.*, 2007).

Thus, in considering dosimetric models, the potentially unique physical and chemical properties of RNP will need to be evaluated and taken into account. In addition, the possibility that biological effects may occur as a result of combined insults from the radiological, chemical and particulate properties of RNP should be investigated. This would necessarily include how such interactions might be additive, synergistic or antagonistic. Ultimately, if such interactions are shown to be likely, then more complex dosimetry models may need to be considered that take into account radiation, chemical and/or particle properties, as well as different uptake pathways (*e.g.*, translocation from olfactory nasal airways into brain *via* olfactory nerves).

6.2 General Approach to Biokinetic Modeling for Intakes of Radioactive Nanoparticles

The dosimetric approaches needed to address intakes of radionuclides, and RNP in particular, are complex because in most cases the deposition of energy per unit mass within the body is heterogeneous in both time and space. Thus, to fulfill the need to calculate organ-level absorbed doses from intakes of any radionuclide, ICRP (2015) and others have employed a modeling approach in which anatomic entities are identified and physically defined such that absorbed doses can be calculated once the spatial and temporal relationships of radionuclide content for both target and source organs have been described and linked to the decay characteristics of that radionuclide.

Figure 6.1 illustrates a generic compartmental model structure that provides a basis for describing the biokinetics of a given radionuclide. Routes of intake include: inhalation, ingestion, transdermal absorption into or through intact skin and absorption from wounds; and can involve the skin, respiratory and GI tracts (peach color) as entry organs into the body. Depending on the physical and chemical properties of the contaminating material, the radionuclide will be absorbed from the intake organs to blood from whence the dissolved material will be taken up by various systemic organs (blue color), depending on the biochemical characteristics of the radionuclide.

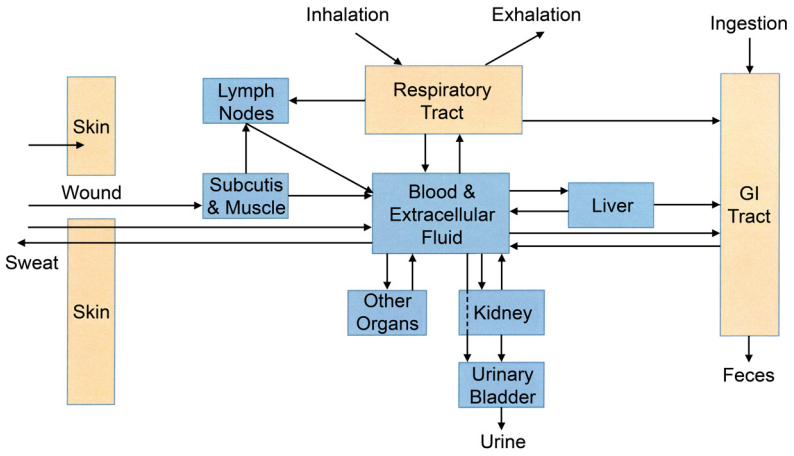


Fig. 6.1. A generic biokinetic model illustrating the compartmentalization of a radionuclide which allows organ-level absorbed doses to be calculated (adapted from ICRP, 1993).

In subsequent sections, biokinetic and dosimetry models will be described for different routes of intakes and their applicability to biokinetics specific to RNP will be considered. The scope of evaluation of the various models for this Report is such that discrepancies are identified in general. Although specific solutions are not offered, the identified areas of concern can provide the basis for follow-up studies in the future.

6.3 Radiation Dosimetry of Inhaled Radioactive Nanoparticles

The standard reference model used for calculating radiation doses from inhaled radionuclides is the HRTM, published as ICRP Publication 66 (ICRP, 1994a). Although other respiratory tract models exist (Miller *et al*., 2016; NCRP, 1997), the HRTM has been used internationally over the last 20 y for calculating dose coefficients for both workers and members of the public for radiation protection, and is used in this analysis. The major components of the HRTM consist of:

- morphometric model of the respiratory tract;
- physiological parameters, which are age- and gender-dependent;
- model for total and regional deposition;
- clearance model; and
- dosimetry model.

Other sections include the radiation biology of respiratory tract cancers and consideration of the behavior of gases and vapors in addition to particulate aerosols. Of these, deposition, clearance and dosimetry modeling are the most important features to be evaluated with respect to RNP.

6.3.1 *Deposition of Inhaled Radioactive Nanoparticles*

ICRP divides the HRTM into four anatomic segments:

- extra-thoracic (ET) region, which is comprised of the head airways and is further divided into nonciliated (ET_1) and ciliated nasal airways plus oral cavity and pharynx (ET_2);
- bronchial region (BB);
- bronchiolar region (bb); and
- alveolar interstitial (AI) region.

For the HRTM, ICRP analyzed and summarized all the human deposition data available at that time, and supplemented these results with measurements of deposition in physical replicas of

human conducting airways (head and thoracic). This included particle sizes extending from 5 nm activity median thermodynamic diameter through 20 μm AMAD. These data were then fitted with a theoretical deposition model (Egan and Nixon, 1985; 1987). The results for regional deposition in the ultrafine particle size range are shown in Figure 6.2.

Of note for the NP size range <0.3 μm is that the predominance of the fractional deposition of inhaled NP is in AI (14 to 50 %), the AI region of the lung. This predominance extends downward in particle size to ~5 nm. Thereafter, smaller sizes are increasingly deposited in the proximal conducting airways such that by 2 nm, maximum deposition occurs in the ET airways. In comparison, for particles having the default particle size for occupational environments of 5 μm AMAD, the predominant fractional deposition is in ET (76 %) with <5 % depositing in AI (ICRP, 1994a). Thus, there is a marked increased tendency for RNP with diameters between ~5 nm and 0.3 μm to deposit in the AI region versus particle sizes more typical of occupational aerosols. Often, the consequence of this is that the dose coefficients for RNP of a given radionuclide will be greater than that for particles of that radionuclide having the larger size of a typical occupational aerosol. For example, the dose coefficient for a 5 μm AMAD polydisperse aerosol of ^{239}Pu, Type M absorption is 3.2×10^{-5} Sv Bq^{-1} intake for an occupational worker. In comparison, the dose coefficient of particles of the same radionuclide and absorption type but a particle size of 0.020 μm activity median thermodynamic diameter is 2.0×10^{-4} Sv Bq^{-1}, which is a factor of 6.3 greater. The increase in dose coefficient is attributable mainly to the increased retention in the whole body due to AI deposition, whether the material is insoluble and resides longer in lung (compared to shorter retention in the BB or bb), or is soluble, in which case the material can translocate to systemic uptake sites.

Both the ICRP (1994a) and NCRP (1997) respiratory tract models indicate that there were adequate experimental data available to enable reasonably accurate predictions of the total respiratory tract deposition of aerosols over a very large particle size range, which included most of the range associated with NP. The difficulties in modeling arise when the total deposition values are separated into the various regional deposition fractions, as these values cannot be measured directly. Therefore, there is uncertainty associated with regional deposition values that cannot be resolved directly from the experimental data.

To illustrate these uncertainties, Yeh *et al*. (1996) compared the regional deposition patterns predicted based on the ICRP (1994a) and NCRP (1997) respiratory tract dosimetry models (Figure 6.3).

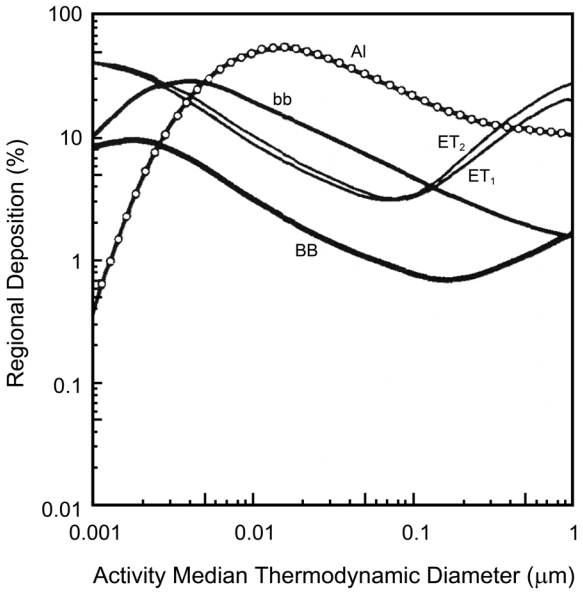


Fig. 6.2. Regional deposition for nose-breathing male worker (ICRP, 1994a).

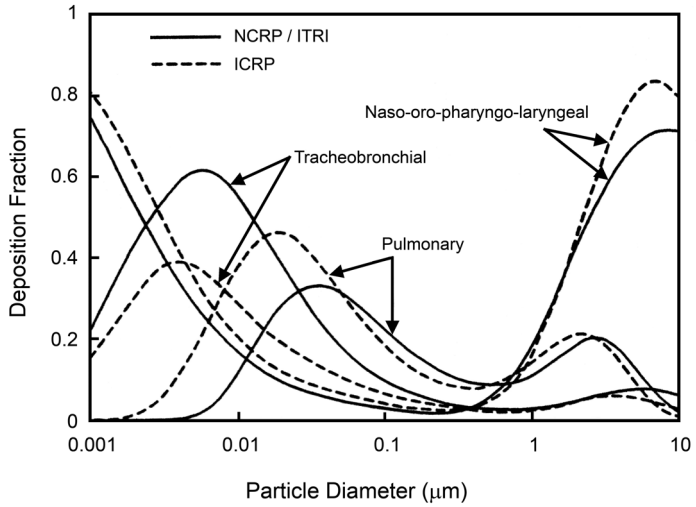


Fig. 6.3. Predicted particle size-dependent deposition patterns in the naso-oro-pharyngo-laryngeal, tracheobronchial, and pulmonary regions for the NCRP/Inhalation Toxicology Research Institute (ITRI) respiratory tract model and for the ICRP respiratory tract model for monodisperse aerosols with a geometric standard deviation of one (Yeh *et al.*, 1996).

Using the following conditions: monodisperse particles of density 1 g cm^{-3}, tidal volume = 770 mL, breathing frequency 13 min^{-1}, functional residual capacity 3,000 mL, the authors noted that deposition in the tracheobronchial region (BB + bb) was significantly greater at sizes ~10 nm for the NCRP model (55 %) than the ICRP model (20 %). Consequently the predicted deposition in the pulmonary region of ~10 % for the NCRP model was proportionately less than the predicted pulmonary deposition of ~35 % for the ICRP model. The respective dose coefficient based on the NCRP model would therefore be lower than the dose coefficient based on the ICRP model. These differences in model predictions are due to the use of different theoretical assumptions in modeling deposition in the diffusion regime, which applies specifically to NP.

6.3.2 *Clearance of Inhaled Radioactive Nanoparticles*

Treatment of clearance of inhaled deposited RNP and other aerosols is an essential component of the HRTM, as it determines the radiation doses to the various regions of the respiratory tract as well as the rates of translocation of radionuclide from the respiratory tract to the GI tract, lymphatic drainage systems and absorption to blood, followed by deposition in other organs (termed systemic organs). Clearance kinetics also determine the pattern of urine and fecal clearance of radionuclides, thus affecting the interpretation of bioassay monitoring data.

The HRTM contains two distinct clearance components: (1) mechanical clearance of particles or other undissolved species from one portion of the respiratory tract to another and clearance ultimately to the GI tract or lymphatics, and (2) dissolution/absorption to blood. Conceptually and mathematically, the two clearance mechanisms are considered to occur simultaneously and competitively (Figure 6.4). Mechanical clearance is considered to occur whether particles are free in airway fluids or inside cells such as alveolar or airway macrophages. The mechanical transfer rates for particles are assumed to be the same for all materials. Thus, implicitly, mechanical clearance is assumed to be independent of particle size, although Oberdorster (1988) points out that alveolar macrophage-mediated clearance is best described when the particles are of low *in vivo* solubility and cytotoxicity.

To accommodate the multiphasic clearance of particles from the HRTM, various compartments have been assigned to represent the anatomic compartments (ET, BB, bb, AI) such that the known time-dependent clearance patterns could be approximated using constant fractional clearance rates, which are then summed to represent the net behavior occurring in a given compartment. In so

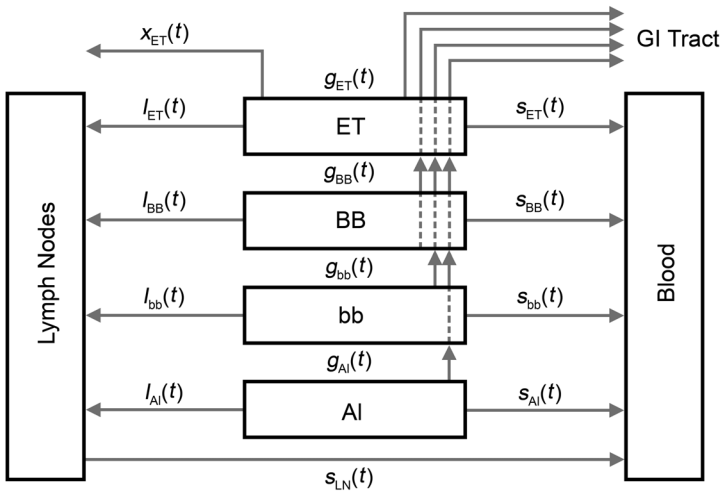


Fig. 6.4. HRTM clearance model illustrating the competitive pathways and time-dependent transfer coefficients for mechanical clearance of particles from the ET region to outside the body and from the respiratory tract to the GI tract and lymph nodes versus solubilization of material to the blood (ICRP, 1994a).

doing, the "shape" of the lung clearance function as it relates to particle size becomes driven by the initial regional deposition pattern.

It can be noted that the NCRP respiratory tract model deals with clearance similarly to the HRTM. In particular, both model clearance as a competition between mechanical clearance and dissolution/absorption; mechanical clearance rates are the same for all materials and dissolution/absorption is the same in all regions of the respiratory tract (with the exception of ET_1 of the HRTM). The ICRP and NCRP models differ mainly in implementation to take account of time-varying clearance rates, in that the HRTM uses multicompartment systems compared with the NCRP approach of using time-varying clearance functions. The results of the two approaches are similar, which is expected since they both model the same data sets.

In terms of modeling dissolution/absorption to blood, the HRTM uses a four-compartment representation of the physicochemical state of deposited particles:

- particles in initial state;
- particles in transformed state;
- bound material; and
- blood-borne radionuclide.

This dissolution kernel is embedded in each of the anatomic compartments that describe the mechanical clearance of particles, giving the model a multidimensional structure that allows for competitive mechanisms. The HRTM assumes that the dissolution behavior of particles is independent of their location within the respiratory tract, with the exception of the anterior nasal airways (ET_1), in which no dissolution is assumed to occur. Because it is recognized that the time-dependent dissolution rates can vary over a large range, the HRTM assumes dissolution rate constants from 10^{-3} to 100 d^{-1}. These fractional rates, when taken in combination and using the four-compartment dissolution model, have been shown to be adequate for describing time-varying dissolution behavior, including increasing and decreasing dissolution patterns.

To accommodate the large range of dissolution/absorption values, the HRTM established three default absorption types: F, M and S, indicating fast, medium and slow dissolution/absorption behaviors. Although these absorption types bear a qualitative relationship to the former ICRP (2000) clearance classes D, W and Y (which indicated clearance half-times on the order of days, weeks and years), they are different in that the former represent only dissolution/absorption whereas the latter model represents overall clearance (both mechanical and dissolution) from the respiratory tract. Briefly, for Type F, there is rapid absorption of almost all radionuclides deposited in BB, bb and AI, and ~50 % of the material deposited in ET_2. For Type M, ~70 % of the AI deposit reaches the blood eventually, 10 % of the deposit in BB and bb are absorbed rapidly as is 5 % in ET_2. For Type S, there is little absorption from ET, BB, or bb, and ~10 % of the radionuclide deposited in AI reaches the blood slowly but eventually (ICRP, 1994a).

For modeling purposes, the HRTM uses particle size to assign the fractional deposition of particles in the individual compartments of the respiratory tract, but the HRTM does not explicitly distinguish clearance rates from those compartments on the basis of particle size. However, ICRP does acknowledge that there are certain properties such as the rate of particle translocation to the alveolar interstitium that have been shown to relate to NP (see Appendix E of ICRP, 1994a). For example, Ferin *et al*. (1990; 1991) found that titanium and aluminum NP (0.02 to 0.03 μm) had greater penetration into the alveolar interstitium than 0.2 to 0.5 μm particles instilled in rats, which led to greater lung retention. ICRP also recognized that absorption to blood also could apply to the transport of particulate material to blood, although this mechanism may only be important for particles smaller than a few nanometers. For example, Smith *et al*. (1977) and Stradling *et al*.

(1978a; 1978b) found that 1 nm particles of $^{239}PuO_2$ or $^{238}PuO_2$ appeared to be readily translocated from the lungs of rats to blood; conversely, plutonium particles >25 nm showed negligible translocation. Additionally, Lauweryns and Baert (1977) observed that intercellular clefts in pulmonary blood capillaries do not exceed 4 nm, suggesting that there would be a barrier against particles larger than a few nanometers for paracellular translocation. Such conclusions about the limited ability of particles to translocate may or may not be valid for long, narrow particles such as nanofibers or nanotubes. Yet with the recent interest in the interactions of ENP with biological systems, there are numerous studies demonstrating translocation of some inhaled ENP to blood circulation and subsequent accumulation in secondary organs and tissues. This literature has been reviewed by Oberdorster *et al*. (2007) and more recently by Balasubramanian *et al*. (2013) and discussed below (Section 6.5.2).

One clearance pathway that is not explicitly considered in the HRTM is the translocation of particles deposited on the olfactory nasal airway surface along olfactory neurons into the olfactory bulb of the brain. This pathway has been well documented in experimental animal models for NP as well as for certain soluble metal compounds such as manganese (Dorman *et al*., 2001; Oberdorster *et al*., 2009). This pathway raises questions relative to both the extent and magnitude of the clearance *via* this route, and the appropriate target cells for dosimetry in the central nervous system. Regarding the latter, there is not good evidence showing that NP that end up in the olfactory bulb translocate further into the brain tissue. If this will be demonstrated, then a new target tissue may need to be considered. The dosimetry in any case will depend on the nature of the radioactive emissions arising from the RNP.

6.3.3 *Respiratory Tract Dosimetry for Radioactive Nanoparticles*

As stated in ICRP Publication 66 (ICRP, 1994a), the purpose of developing the dosimetry model in the HRTM was to evaluate doses to the various tissues of the respiratory tract. To do this, the HRTM took a new approach to defining what absorbed doses should be calculated (*i.e*., what tissues were at risk). In so doing, they identified six target tissues:

- keratinized epithelium of the skin of the anterior part of the nose;
- stratified squamous epithelium of the main ET airways;
- ciliated epithelium of the bronchi;
- ciliated epithelium of the bronchioles;

- alveolar-interstitium; and
- thoracic and ET lymph nodes.

By selecting the six target tissues, the HRTM established a basis for creating geometric models to be used in calculating the radiation doses. Selection was based on the known or hypothesized cell populations at risk for induction of respiratory tract cancers, and their locations within the respiratory tract tissues were used to define the geometry for dose calculation. For example, Figure 6.5 illustrates the cylindrical geometry used for calculating doses for the conducting airways, and Figure 6.6 shows the dimensions used for defining the location of the target cells within the stratified epithelium of the bronchi (basal and secretory cells), as well as the dimensions of the other tissue compartments needed for calculating the patterns of energy absorption within these structures. Thus, for ET, BB, and bb, doses are calculated as absorbed doses to the target cell populations at risk averaged over the geometrically defined volumes that contain the target cells. For the AI and lymph nodes, the absorbed dose is averaged over the total volume of the respective compartment.

Although the HRTM does identify the club cells (formerly known as Clara cells) in the respiratory bronchioles and the Type II epithelial cells in the alveoli as the critical cells at risk, it is assumed that the cells are uniformly distributed throughout the tissue, and hence the average absorbed dose is calculated for the whole tissue.

How do these dosimetric models of the respiratory tract impact the way that doses would be calculated for RNP? The deposition of RNP in the total respiratory tract is considered to be adequately

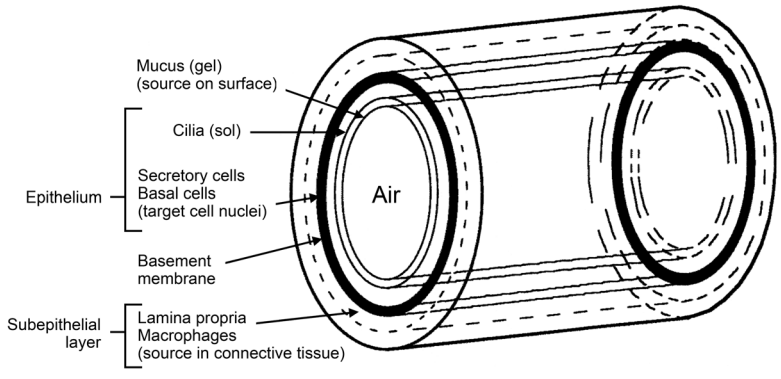


Fig. 6.5. HRTM cylindrical geometry for conducting airways (ICRP, 1994a).

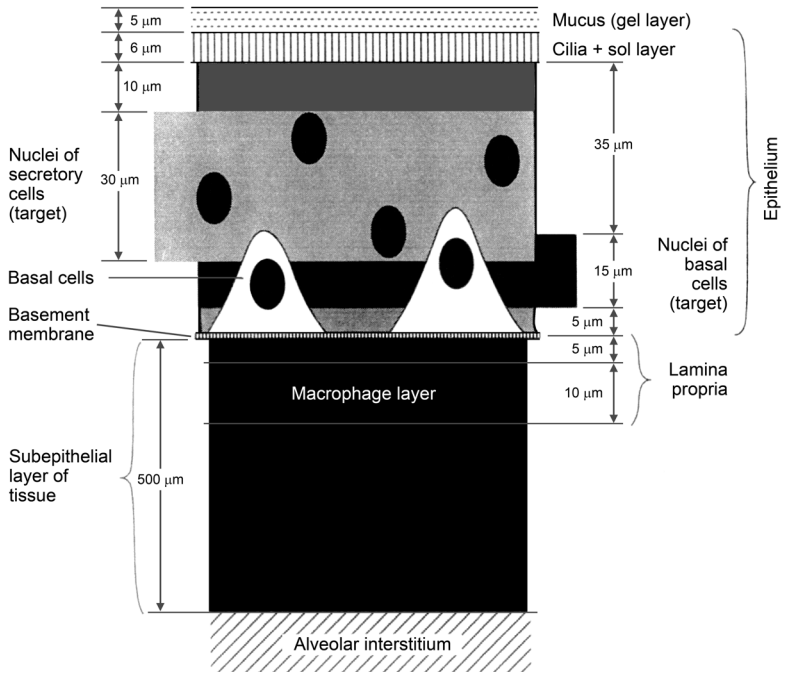


Fig. 6.6. Geometry of bronchial epithelium showing location of target cells for calculating dose (ICRP, 1994a).

modeled using the structure, parameters, and parameter values from the HRTM. However, modeling of regional deposition, particularly in the BB but in downstream regions as well, is more uncertain because of the lack of adequate experimental data. It is estimated that the deposition uncertainties may be on the order of a factor of two. These uncertainties merit additional investigation.

As far as clearance is concerned, the translocation of intact, insoluble NP to blood circulation and subsequent accumulation in systemic organs represents a novel clearance pathway for varying fractions of NP depending on their physicochemical properties. This may well affect the dosimetry, particularly, in those secondary organs, because these organs are only exposed to NP but not to micrometer-sized particles following inhalation of low concentrations. Thus, physical translocation of NP from deposits in the respiratory tract is a novel pathway for NP that needs to be considered in a new HRTM. As an example, if there is a significant amount of RNP that migrate and reside in the interstitium of either conducting airways or AI, and the distribution is highly nonuniform, then the present approach of averaging dose, particularly to the AI, may

not be adequate. Presently, however, there is inadequate information for NP to indicate how radiation doses would need to be calculated for secondary target tissues.

6.4 Radiation Dosimetry of Ingested Radioactive Nanoparticles

The current dosimetry model dealing with ingested radionuclides is that described in ICRP Publication 100 (ICRP, 2006a). This HATM, which replaced the model adopted in ICRP Publication 30 (ICRP, 1979), provides for age-dependent dosimetry, and calculates radiation doses for all regions of the GI tract, *viz*., oral cavity, esophagus, stomach, small intestine, and colon. The HATM, which is shown schematically in Figure 6.7, is more realistic physiologically than that of ICRP Publication 30 (ICRP, 1979), and provides more anatomic structure to allow calculation of doses at the tissue level. In addition, differentiation of organ contents from the respective tissue compartments allows for uptake and retention of radionuclides within specific tissues of the human alimentary tract (HAT), which then segregates radionuclides that exist in contents from those bound to HAT tissue. This differentiation is important in more realistic calculations of radiation doses from radionuclides in these two source compartments. Note that the organs and fluids illustrated in Figure 6.7 as dashed boxes are not part of the HATM but are included to show connections between the HATM, HRTM, and systemic biokinetic models. This total view of the connectivity between compartments enables realistic assessments of factors such as how the propensity of inhaled NP to deposit by diffusion in the head airways makes NP more available for mechanical clearance to the GI tract.

The HATM considers several biological processes that impact the dosimetry of ingested radionuclides. These include entry into the oral cavity by ingestion or the esophagus *via* mechanical clearance of aerosols from the respiratory tract, radionuclide deposition/retention on or between teeth with return to the mouth, deposition/retention on the mucosa of the walls of stomach and intestines, transfer from the mucosa back to the lumen or to blood, and transfer from various secretory organs or blood into the lumen of the HAT. In general the biokinetics of radionuclides in the HAT are described by first-order rate constants, recognizing that this assumption simplifies the complex processes involved in transfer of material through the HAT lumen. Parameter values describing the transfer of material between compartments mostly consist of generic values with the exception of some radionuclides for which more information is available, and that permit the use of element-specific values.

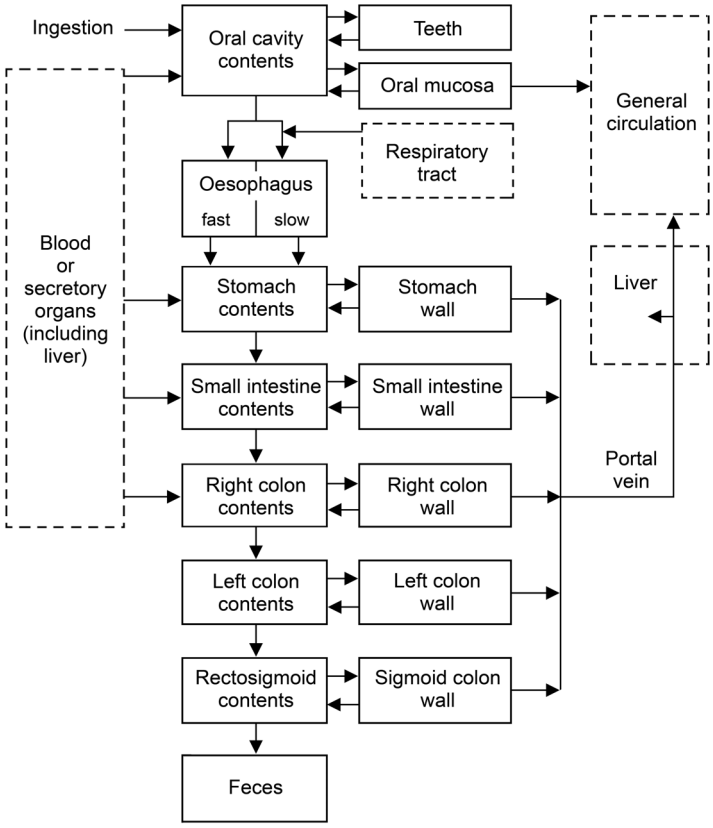


Fig. 6.7. ICRP Publication 100 HATM schematic (ICRP, 2006a).

Regarding the absorption of NP from the GI tract to other organs, Appendix B.3 provides information about a number of studies that have been conducted with a range of NP, including RNP, in mice, rats and humans. As indicated by that work, absorption of intact NP from the GI tract does not appear to occur at more than fraction-of-a-percent amounts.

In terms of dosimetry, HATM has taken an approach similar to that used by the HRTM (*i.e.*, doses are calculated to target tissues that consist of defined geometric structures purported to contain the cells at risk to the induction of radiation-induced cancer). For example, the cylindrical geometry used for dosimetry of the tubular HAT organs is illustrated in Figure 6.8, and the substructure identifying the location of the target cells in the small intestine (*i.e.*, the stem cells responsible for renewing and maintaining the crypt epithelium) is shown in Figure 6.9. Thus, radiation energy deposited

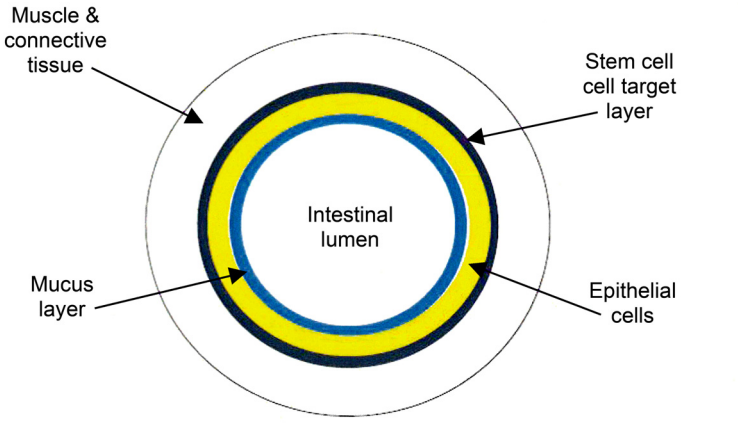


Fig. 6.8. Cylindrical geometry used for tubular HATM organs (ICRP, 2006a).

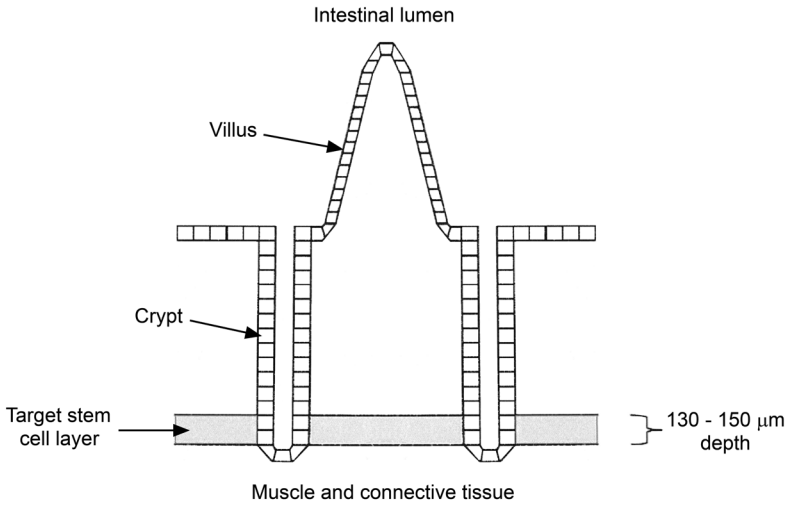


Fig. 6.9. Geometric model of target cells in the small intestine (ICRP, 2006a).

within this target tissue from sources of radionuclides contained within the small intestinal contents, the epithelial and subepithelial tissues, and tissues and organs exterior to the small intestine are calculated and summed to yield the absorbed radiation dose to the small intestine. Similar approaches are used for calculating doses to the other targets within the HATM. In all cases, the doses to the target tissues are doses averaged over the volume and mass of the target tissue; therefore, any potential heterogeneities of energy deposition within a target tissue are not considered.

In general the HATM is relatively silent on issues that might relate to RNP, as it considers intakes to involve the distribution of radioactive species among the bulk material present in the HAT. As such, particle size (with the exception of ingestion of "hot particles," typically >100 μm) is not considered to be an important factor affecting either the distribution within the HAT contents or the absorption to blood (a function of chemical form). It is therefore not clear whether there are attributes of ingested RNP that might affect the applicability of the HATM or its default parameter values. This may require additional study.

On the other hand, the HATM acknowledges that "…materials including macromolecules and small particles also may enter epithelial cells by pinocytosis…" (ICRP, 2006a). This phenomenon has been shown for both normal epithelial absorptive cells as well as the lymphoid M cells of Peyer's patches. The report goes further to indicate that while this uptake pathway to interstitial sites is not a major contributor in adults, it does provide a mechanism for acquisition of passive immunity in neonates (ICRP, 2006a).

6.5 Radiation Dosimetry of Radioactive Nanoparticles for Intact Skin

NCRP Report No. 156 (NCRP, 2006) provides general guidance on calculating radiation doses to intact skin. The guidance involves the use of a number of previously published models (Chaptinel *et al*., 1988; Kocher and Eckerman, 1987; NCRP, 1989c; 1991; 1999). Additionally, information on the calculation of radiation doses to skin from fallout particles is available in Apostoaei and Kocher (2010). Concerns in these reports focus mainly on beta- and gamma-emitting radionuclides because alpha radiation is absorbed by the epidermis before it can reach live tissue.

Current information on the ability of NP to enter skin involves studies with nonradioactive nanomaterials. Some studies suggest that nanomaterials could potentially enter the body through the skin during occupational exposure. Tinkle *et al*. (2003) have shown

that particles smaller than 1 μm in diameter may penetrate into mechanically flexed skin samples. Ryman-Rasmussen *et al*. (2006) have reported that quantum dot NP of different size, shape, and surface coatings with varying physicochemical properties were able to penetrate the intact skin of pigs. The quantum dots were reported to penetrate the stratum corneum barrier by passive diffusion and localize within the epidermal and dermal layers within 8 to 24 h. The dosing solutions were two- to fourfold dilutions of quantum dots as commercially supplied and thus represented occupationally relevant doses. Note that penetration was "into" but not "through" the skin.

As summarized by NIOSH (2009), at this time it is not fully known whether skin penetration of NP would result in adverse health effects in exposed animal models or humans. However, the topical application of raw SWCNT to nude mice has been shown to cause dermal irritation (Murray *et al*., 2007). Studies conducted *in vitro* using primary or cultured human skin cells have shown that both SWCNT and MWCNT can enter cells and cause release of proinflammatory cytokines, oxidative stress, and decreased viability (Monteiro-Riviere *et al*., 2005; Shvedova *et al*., 2003). Lademann *et al*. (2015) reported that hair follicles are a target for the accumulation of NP in skin. It remains unclear, however, how these findings may be extrapolated to a potential occupational risk, given that additional data are not yet available for comparing the cell model studies with actual conditions of occupational exposure.

Research on the dermal exposure to nanomaterials is ongoing. Study needs include investigations of RNP behavior in intact skin. Potentially related issues are:

- rate of interception and retention of airborne NP on skin or clothing, including the effects of moisture on skin or clothing in enhancing interception and retention;
- penetration of airborne NP or surface-deposited NP through clothing;
- penetration of NP into skin following deposition (*e.g*., *via* pores or hair follicles);
- efficiency of wiping, washing or bathing in removing NP from skin over time; and
- estimation of doses to radiosensitive tissues of skin when RNP have penetrated to sufficient depths in those tissues to deliver radiation doses (a question that is especially important for alpha-emitting radionuclides).

6.6 Radiation Dosimetry of Radioactive Nanoparticles in Wounds

Consensus human dosimetry models for inhaled and ingested radionuclides have existed for over 50 y. However, such a model had never been developed and agreed upon for intakes *via* wounds until NCRP, in collaboration with ICRP, formulated such a biokinetic and dosimetric model (NCRP, 2006). Unlike the ICRP and NCRP inhalation and ingestion models, the NCRP wound model was conceptualized and parameterized almost exclusively using experimental animal data because the large majority of human exposure cases also involved the use of surgical excision of contaminated wound sites as well as chemical decorporation. Therefore, unperturbed biokinetic data in humans was not readily available.

Figure 6.10 provides a schematic of the NCRP wound biokinetic model. The model was conceived using knowledge of the chemical and biological properties of the contaminating radioactive materials, whether they are soluble, colloidal, particulate or fragment forms. The model also considered the biological response of the host tissue to the presence of foreign bodies or material (*i.e.*, capsule formation). Experimental animal data from studies that involved the injection of relatively soluble forms of 48 radioelements were used to specify four categories of *in vivo* solubility (*i.e.*, weak, moderate, strong and avid). These elements comprised all the chemical families except the noble gases. For the less soluble colloidal, particulate and fragment forms, most of the available data dealt with uranium, plutonium, americium, and nuclear weapons test debris. Movement of radionuclides from the wound-site was provided by links to blood and lymph nodes, the former providing the link with the appropriate radioelement-specific systemic biokinetic model. In aggregate, the data were sufficient to parameterize the five-compartment wound-site model adequately.

Dosimetry for radionuclide-contaminated wounds involves two parts: (1) estimation of the committed absorbed organ doses and effective dose from materials translocated from the wound-site and (2) assessment of the absorbed radiation dose to the tissues immediately adjacent to the wound site. The five-compartment biokinetic model provides the mechanism for describing the time-related movement of radionuclides from the wound-site to the systemic organs and tissues, from which equivalent and effective doses are calculated. To calculate local radiation doses to the wound-site, NCRP adopted a number of published dosimetry models commonly used in health physics. These models covered dosimetry for skin or shallow dose (NCRP, 1989c; 1999), and for deeper penetrating wounds involving line and volume sources (*e.g.*, Piechowski and

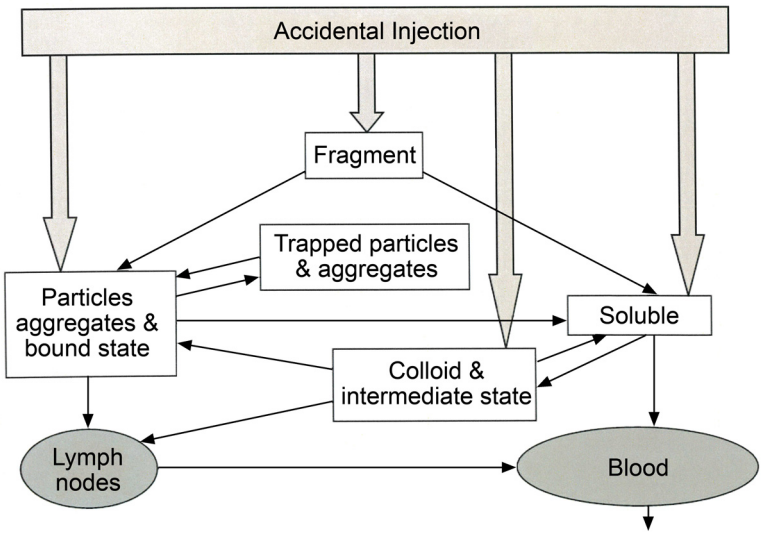


Fig. 6.10. NCRP Report No. 156 wound biokinetic model schematic (NCRP, 2006).

Chaptinel, 2004). No assumptions are made by NCRP about target cell populations at risk. Instead radiation doses are calculated as averages of energy deposited in volumes of tissue considered appropriate to the types of radiation emissions for a given radionuclide. For example, for ^{239}Pu, an alpha-particle-emitting radionuclide, the volume for dose calculation would be taken to be the volume that contains the radionuclide (^{239}Pu alpha particles have a range of ~35 μm in soft tissue). In the absence of other data, a volume of 1 cm^3 is assumed.

The most common types of radionuclide-contaminated wounds have occurred in the nuclear weapons industry in which workers have become contaminated with various physicochemical forms of plutonium. More recently, soldiers in the Operation Desert Storm campaign during the first Persian Gulf War received DU shrapnel wounds. For both of these scenarios, the contaminating materials had typical particle sizes significantly larger than that for RNP, up to gram amounts per fragment. Nevertheless, the NCRP wound model did address the expected behavior of small particles as part of its consideration of the retention and clearance of particles from wound sites. For example, the model described that tissue or interstitial macrophages can recognize and engulf solid particles with sizes from ~0.01 to 20 μm (Snipes, 1989). On the other hand, apparently all sizes of particles are not phagocytized with equal

efficiency. Sanders (1967) showed that larger particles of PuO_2 are phagocytized by peritoneal and alveolar macrophages more efficiently and rapidly than smaller particles (*i.e.*, 0.08 to 0.75 μm). Additionally, at long times after injection in rats, Hahn *et al*. (2002) showed that 0.005 to 0.01 μm particles of Thorotrast® [a colloid of thorium dioxide used as a contrast medium in cerebral angiography (VanHeyden Company, Dresden-Radebeul, Germany)] suspension were almost entirely found within macrophages in the connective tissue between the muscle bundles at or adjacent to the original injection site. Readily detectable amounts of Thorotrast® also could be detected at 1 to 2 y in the lymph nodes that drained the injection site (Hahn *et al*., 2002). Harrison *et al*. (1978) noted in rats injected with 1 nm PuO_2 particles that there was rapid translocation from the wound site, that there was only a minor amount taken up in lymph nodes, and a significant amount of plutonium was excreted in urine. The authors speculated that their injected particles may have been too small to be phagocytized by macrophages and instead translocated as intact NP. They also are believed to be small enough to be filtered through the glomeruli of the kidney and appear in urine (Berliner, 1973).

Presently it appears that the structure of the NCRP wound model should be adequate to accommodate the unique features of RNP retention in and clearance from wounds. In some cases, new parameter values may be required to fit existing data, but this is always the case when dealing with specific materials and radionuclides.

6.7 Biokinetics of Nanoparticles that Affect Internal Dosimetry

In the currently accepted radiation dosimetry models for intakes of radionuclides that were described above, several characteristics of NP and RNP were briefly mentioned. In this section these unique biokinetic properties will be elaborated on and compared with the default assumptions in the various dosimetry models. Since most of the NP research has involved inhalation exposure, a similar focus will be adopted here.

6.7.1 *Regional Deposition of Radioactive Nanoparticles*

By design, the respiratory tract dosimetry models of both ICRP and NCRP partition the respiratory tract into distinct anatomic sections, which then require that regional deposition fractions be provided explicitly for dosimetry calculations. However, as stated by ICRP (1994a): "…in the main, experimental data are still available only for the adult Caucasian male, and for a limited range of

particle size (from ~1 to 10 μm aerodynamic diameter), whereas the application of the human respiratory tract dosimetry model is required to be much broader." Furthermore, it also is acknowledged that most of the empirical data are based on measurement of deposition in the total respiratory tract or total thoracic region. Consequently, regional deposition beyond the head airways is inferred based on functional assumptions on clearance (*e.g.*, that particles deposited in the bronchial airways are cleared by mucociliary clearance from the lung most rapidly, followed by bronchiolar clearance and then alveolar clearance).

Since the publication of the ICRP and NCRP reports, newer data have been published on regional deposition. For nasal airway deposition, studies have been done in which NP (or ultrafine particle) deposition has been measured *in vivo* (Cheng *et al.*, 1996a; 1996b) or in anatomically accurate nasal airway replicas (Cheng *et al.*, 1988; Guilmette *et al.*, 1995; Kelly *et al.*, 2004; Swift *et al.*, 1992). Given the range of experimental designs used and the variability in human subjects, it has been reassuring to learn that the measured deposition patterns have been reasonably consistent and could be modeled by simple relationships between diffusion coefficient and flow rate (Cheng *et al.*, 1988).

For deposition of NP in the respiratory tract distal to or including the nasal airways, most of the studies have been performed such that only total deposition was determined directly, usually by measuring inspiratory and expiratory aerosol concentrations and correcting for experimental line losses (*e.g.*, Beckett *et al.*, 2005; Heyder *et al.*, 1975; 1986; Muir and Cena, 1987). Thereafter, partitioning deposition into the ET, bronchial, and alveolar compartments is done using a combination of data analysis based on retention times and deposition modeling, which can be empirically based or theoretical, using the various deposition mechanisms and geometric models of the lung anatomy. The latter approach becomes somewhat simplified for NP < 100 nm because diffusion mechanisms predominate over sedimentation and impaction (ICRP, 1994a).

6.7.2 *Biokinetic Characteristics of Inhaled Radioactive Nanoparticles*

The most prominent difference between the early fate of inhaled deposited micrometer-sized particles and NP results from the fact that essentially all micrometer-sized particles are phagocytized by epithelial surface macrophages (both alveolar and airway) within several hours after deposition under physiological conditions while a significantly smaller fraction of NP are phagocytized by airway

and alveolar macrophages in that same time frame (Kreyling *et al*., 2013). This difference gives rise to uptake by epithelial cells, which opens pathways of translocation into the lung interstitium and uptake of particles into the blood and lymph circulation. As indicated by results from rat studies, retention in the interstitium allows for re-entrainment of NP onto the respiratory epithelium either by interstitial macrophages or *via* the bronchus-associated lymphoid tissue (Ferin and Oberdorster, 1992b; Ferin *et al*., 1992; Semmler-Behnke *et al*., 2007). This in turn is followed by subsequent macrophage-mediated transport up the mucociliary escalator to the larynx from where the NP are swallowed into the GI tract, a process similar to the airway clearance of micrometer-sized particles.

Translocation of NP across the ABB into blood circulation is rather low, although it is greater for lymph node translocation. For example, results from rat studies have shown that translocation to secondary organs can be as high as 10 % of the peripheral lung deposit for inhaled 20 nm iridium NP or 1 to 2 % for inhaled 20 nm titanium dioxide NP or inhaled 20 nm gold nanoparticles (GNP), but also is 10 % for instilled 1.4 nm GNP, demonstrating the importance of the physicochemical properties of the NP (Kreyling *et al*., 2014). Translocation and clearance to lymph nodes following repeated inhalation exposure of rats to nanometer-TiO_2 or MWCNT is higher, up to 16.7 % about 1 y after the end of the exposure (Mercer *et al*., 2013; Oberdorster *et al*., 1994). However, it has to be considered that in both studies very high exposure concentrations had been used which may have increased interstitial access and subsequent clearance into lymphatics.

Translocation across barriers is an important transport mechanism that has been reported in numerous papers. Even at low doses, evidence of translocation across the ABB is unique to NP and such translocation has not been reported for micrometer-sized particles except for conditions of extremely high lung overload (Kreyling *et al*., 2013). Comprehensive lists of translocation studies have been provided by Balasubramanian *et al*. (2013) and Oberdorster *et al*. (2005). Additionally, translocation across the ABB depends on physicochemical parameters of the NP such as size, material, surface charge, and likely other parameters (Geiser *et al*., 2005; 2013; Kreyling *et al*., 2002a; 2009; 2013; Schleh *et al*., 2012; 2013; Semmler *et al*., 2004; Semmler-Behnke *et al*., 2007), and importantly, the delivered dose and dose rate.

Since NP translocation biokinetics are completely different from the rates s_{AI}, s_{bb}, s_{BB}, and s_{et} as defined for dissolved material in the HRTM (ICRP, 1994a), additional transport pathways and rates

specific for NP translocation across the ABB should be included in a new HRTM. These new rates would be dependent on particle size, material and other physicochemical particle properties. Translocation across the respiratory tract epithelium is very likely to occur in all four compartments (*i.e.*, ET, BB, bb, and AI) but basically is only relevant for AI due to its much larger surface area. This novel pathway has only been reported for NP so far, and for micrometer-sized particles only at excessively high doses relevant to conditions of lung particle overload. Hence, potentially significant accumulation of RNP in secondary organs is an important consideration that needs to be addressed in an updated model.

A proposed expanded HRTM taking into account the role of translocation in respiratory tract clearance of RNP is shown in Figure 6.11. Additional transport rates [*i.e.*, $m_{ET}(t)$, $m_{BB}(t)$, $m_{bb}(t)$, and $m_{AI}(t)$] are proposed between each of the lung compartments in the current HRTM and blood. Also, translocation can occur *via* neurons from the upper respiratory tract and tracheobronchial region (Oberdorster *et al.*, 2009) (see following section for additional discussion).

Regarding radiation dosimetry, the HRTM provides sufficiently precise estimates for short-term exposures, notwithstanding the uncertainties in regional respiratory tract deposition. However, during chronic exposure conditions the additional accumulation of poorly soluble NP in secondary organs is critical and needs to be addressed in future reports. Obviously, additional knowledge about accumulation kinetics (buildup and clearance) in secondary organs is essential.

For NP consisting of or carrying soluble or leachable metal-based radionuclides in blood, the dissolution rate can vary significantly, depending on whether they are rapidly, moderately or poorly soluble materials. The products released from NP (*i.e.*, metal ions after dissolution or atoms and/or molecules after degradation) may be rapidly bound by or incorporated into blood and plasma proteins and lipids. As a result, their ultimate biokinetic fate is determined by their new carrier.

Proteins and lipids in plasma or cytosol are likely to adsorb to the undissolved NP, as well as to insoluble NP *per se*. This depends strongly on the physicochemical properties of NP surfaces as shown in several *in vitro* studies (Cederval *et al.*, 2007; Fertsch-Gapp *et al.*, 2011; Monopoli *et al.*, 2011; 2013; Schaffler *et al.*, 2013; Walczyk *et al.*, 2010). This so-called "corona" has been found to be dynamic using *in vitro* studies as highly abundant proteins like albumin may bind first but get replaced by less abundant yet high-affinity proteins, and the composition can change when translocating from blood to other body compartments and extra- and intracellular fluids.

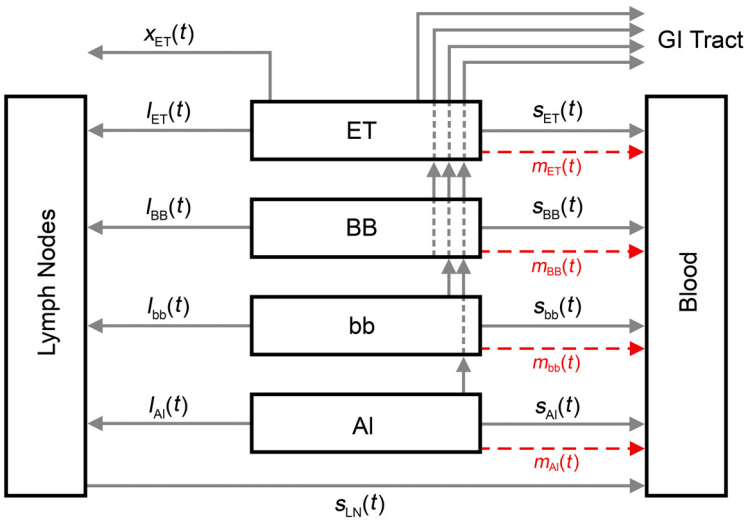


Fig. 6.11. Proposed HRTM clearance model modified to account for the role of translocation of intact RNP across the ABB into the blood circulation. The differential biokinetic behavior of RNP versus soluble radionuclides in the blood will need to be accommodated in the corresponding systemic biokinetic model (adapted from ICRP, 1994a).

The protein corona, formerly described as opsonization, can mediate or facilitate endocytosis by phagocytic cells of the Mononuclear-Phagocyte System and be retained mainly in organs such as liver, spleen, and bone marrow but also in other organs and tissues (*e.g.*, lungs, heart, brain, kidneys, muscle, lymphatic tissue) because of their resident tissue macrophages. Inside those phagocytic cells NP are contained in phagolysosomal vesicles in which NP are subject to further enhanced dissolution due to the acidic lysosomal pH value of about five. In addition to phagocytosis, in principle all cells can endocytose NP depending on their protein corona and the physicochemical properties of NP. Undissolved NP may be retained long-term in various organs and tissues. Part of the clearance of those long-term retained NP is likely to involve extravasation and translocation *via* lymphatic circulation to local lymph nodes.

With respect to elimination from the body, clearance from liver *via* bile into the intestinal tract has been reported repeatedly in the literature. This hepatobiliary clearance pathway can only be determined after intravenous application of the particles, since application to the lungs would not allow dissecting hepatobiliary clearance from other pathways such as particle transport from the lung

periphery to the larynx and then into the GI tract. This hepatobiliary clearance has not been reported for micrometer-sized particles. It seems to correlate with decreasing NP size (Hirn *et al*., 2011) and is likely to depend on other physicochemical NP properties. Yet, only a small fraction of NP retained in the liver are cleared by this pathway, as determined in rodent studies (Hirn *et al*., 2011; Schaffler *et al*., 2014).

Another important clearance pathway for NP present in the circulating blood is urinary excretion *via* the kidney glomeruli. However, this clearance is size-limited, as shown by studies where the surface of NP was engineered to exclude serum-protein binding and thereby preventing NP growth (*e.g*.,by zwitterionic surface modifications). Results showed that NP of sizes <5 to 8 nm are quantitatively excreted in urine (Choi *et al*., 2007; Hainfeld *et al*., 2004). When the corona formation was not explicitly excluded, then the excreted fractions in urine were much smaller, but one study showed that even small fractions (0.4 %) of 80 nm sized GNP were found in the urine of rats following intravenous NP injection (Hirn *et al*., 2011).

There are many open questions about the role of the protein corona on the surface of NP and its composition and dynamics in various biological surroundings. Indeed, when comparing the biokinetics of the same set of negatively charged and monodisperse GNP (*i.e*., ranging from 1.4, 2.8, 5, 18, and 80 nm diameters of the gold core) either after intravenous injection or after intratracheal instillation, the biodistribution of those GNP that crossed the ABB of the lungs as a first step accumulated very differently and highly significantly from those GNP that had been directly injected intravenously (Hirn *et al*., 2011; Kreyling *et al*., 2014). This difference is a strong hint towards the dynamic changes of the protein corona during NP translocation across the ABB. Yet the difference between the more gradual NP translocation across the ABB into blood compared to the bolus delivery of intravenously injected GNP also may be affecting the observed differences in biodistribution indicating that the dose rate of NP delivery is extremely important.

6.7.3 *Biokinetics Example: Monomeric and Polymeric Plutonium*

As described above, there are two aspects of RNP that should be dealt with from the biokinetic/dosimetric perspective. The first is the behavior of RNP at the deposition site (*e.g*., respiratory tract for inhalation and wound sites), and the behavior of RNP that translocate from the deposition site and are absorbed in blood as particles. In the 1960s and 1970s, many experimental studies were conducted in which particulate forms of plutonium were injected intravenous mainly into mice and rats. In the earlier of these studies,

various chemical forms of plutonium were used (*e.g.*, chloride, nitrate or carbonate), but when the pH of the solutions were raised to near neutral conditions, it consequently resulted in the production of hydroxide species that tended to form polymers in suspension (summarized in Table 6.1 of ICRP, 1972). Later experimenters developed methods for deliberately producing polymeric plutonium (Pu-P), whose particle size distributions were reasonably well characterized and reproducible, as a model of blood-borne actinides (*e.g.*, Lindenbaum *et al.*, 1968; Markley *et al.*, 1964).

Data from a study in dogs injected intravenously with either monomeric, soluble plutonium citrate (Pu-M) or Pu-P are used here to illustrate the differences in biokinetics between soluble and particulate plutonium that reaches the blood (Stevens *et al.*, 1975). Less than 0.2 % of the Pu-P used in their study was ultrafilterable through a filter with pore size of 10 nm, with the remainder having a size range of 25 to 800 nm (Stevens *et al.*, 1975). After initial injection, the clearance patterns of Pu-P and Pu-M from blood were very different. At 5 min after injection, only 1.1 % of injected Pu-P was measured in blood compared with 70 % for Pu-M. At 24 h, 0.1 % Pu-P and 30 % Pu-M were present in blood. Concomitantly, the uptake and distribution of plutonium in soluble and particulate forms also were very different (Table 6.1). For Pu-M, the distribution was similar to that measured in other studies and in other species, with the preponderance of Pu-M being measured in skeleton [48.9 % injected dose (ID)] and liver (32.5 % ID) at 14 d after injection. Additionally ~11 % ID was excreted in urine (3.4 % ID) and feces (7.6 % ID). On the other hand, uptake of Pu-P from blood was predominant in tissues rich in reticuloendothelial cells, whose function is to phagocytize blood-borne particulates like bacteria. At 14 d, 68.2 % ID was measured in the liver, 9.4 % ID in spleen (compared with 0.8 % for Pu-M), and 2.2 % ID for skeleton (shown autoradiographically to be in marrow, see below). Additionally only 0.04 % ID was excreted in urine and 0.07 % ID in feces, indicating a lack of clearance of the Pu-P from the body.

Autoradiographs of the plutonium distribution in bone and liver from the dogs injected with Pu-M and Pu-P supplemented the tissue-level information and showed that the distributions of the soluble and particulate forms were significantly different (Figure 6.12) (Stevens *et al.*, 1975). In the liver, plutonium administered in soluble form was approximately uniformly distributed in the parenchymal liver, and associated primarily with hepatocytes; on the other hand, Pu-P was observed to be primarily in liver sinusoids, probably associated with Kupffer cells, and in aggregated or particulate form. In bone, Pu-M was observed to be primarily deposited on the

TABLE 6.1—*Distribution of soluble and particulate plutonium in the dog 14 d after intravenous injection (Stevens et al., 1975).*

Tissue	Pu-M	Pu-P
Liver	32.5	68.2
Spleen	0.8	9.4
Skeleton	48.9	2.2
Soft tissues	1.6	13.8
Cumulative urine	3.4	0.04
Cumulative feces	7.6	0.07

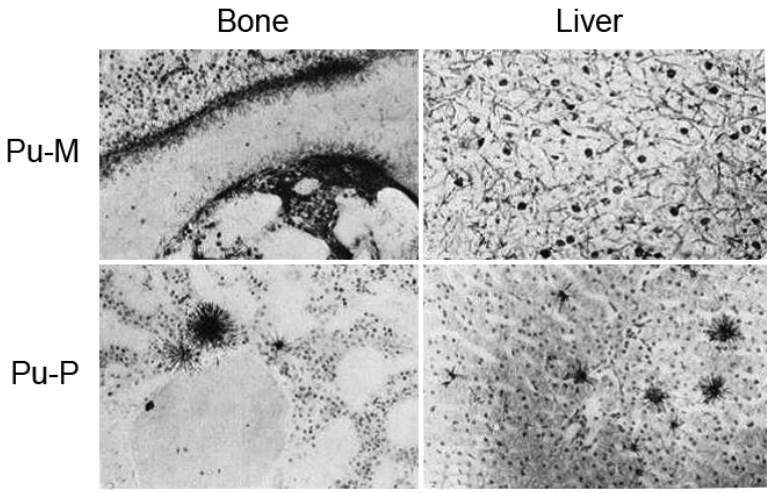


Fig. 6.12. Autoradiographic distribution of plutonium in canine bone and liver tissue after administration in soluble, monomeric (Pu-M) or particulate (Pu-P) forms (Stevens *et al.*, 1975). Magnification factors for the photoelectron micrographs are ~250 times.

mineralized endosteal bone surfaces, whereas Pu-P was noted mainly within the bone marrow volume and again present in aggregate/particulate form.

Thus not only were there significant differences in the biokinetic behavior of Pu-M and Pu-P in blood and the systemic tissues, but there also were differences in where plutonium deposited at the cellular levels in the principal target tissues. Both of these types of differences will need to be taken into account in biokinetic and dosimetric models that deal with RNP. This will require modifications potentially to both parameter values of existing models as well as structural modifications. For example, it may be necessary to track both soluble and particulate forms of a radionuclide that reaches the blood, since both the rate of translocation, the target tissues, and the subsequent retention in the latter will be different. The differences also may relate to how radiation doses are calculated, particularly for alpha-emitting radionuclides.

7. Dose Assessment and Medical Management for Individuals Exposed to Radioactive Nanoparticles

7.1 Approaches for Dose Assessment

The principles and practices of radiation dose reconstruction or dose assessment differ significantly depending on the radiation source, the target individuals, or populations being considered. For example, retrospective dose assessment applied to exposed populations such as the Hiroshima/Nagasaki atomic-bomb survivors for epidemiological purposes will differ markedly from assessments done on workers in nuclear industries such as DOE weapons laboratories, in which exposures to radiation and radioactive materials can be envisioned under both routine and accident conditions. Further the atomic-bomb survivors were exposed acutely to radiation with no or minuscule inhalation of radioactive materials.

NCRP Report No. 163 (NCRP, 2009d) described extensively the methodologies appropriate for dose assessment for a wide range of exposure scenarios. In dealing with these scenarios, the report identified a series of essential steps that were in common regardless of scenario:

1. Define the exposure scenario in terms of individuals or populations, their activity patterns relative to the radiation exposure, and the characteristics of the radiation sources.
2. Identify the exposure pathways in terms of external exposure fields, both spatially and temporally, and internal exposure *via* inhalation, ingestion, or skin contamination and absorption.
3. Develop and implement methods for estimating dose by selecting an appropriate dose metric, data, and measurements relevant to the exposure and models to bridge the data with the ultimate dose.

4. Evaluate the uncertainties in dose estimates.
5. Interpret and present the analyses and results to the appropriate stakeholders.

7.2 Occupational Exposure and Dose Assessment Scenario: Plutonium Processing Facility

To illustrate some principles of dose assessment planning and implementation, consider a nuclear facility in which plutonium is processed radiochemically into several physicochemical forms of varying composition, size and solubility characteristics. The facility contains sufficient quantities of plutonium such that there are risks for routine external radiation exposure in the workplace, neutron/gamma ray exposure from criticality incidents, and accidental intakes of plutonium, mainly by inhalation or wounds. As part of the design of such a facility, substantial effort will be made to minimize the risk of worker exposure through the design of an effective radiation safety program. As described in some detail in Section 5, such changes will rely on the use of the principles of hazard elimination by process design; substitution of low for high hazard operations; engineered controls to minimize exposure; administrative implementation of procedures, policies and training; and implementation of PPE when potential exposures are unavoidable or there is a relatively high risk of occurrence.

As a result of a well-implemented radiation safety program, several types of exposure/dose measurement data will be available to the dose assessor, and additional measurements also should be made when accidental exposures occur. In a plutonium processing facility, radiation detection instruments will be installed in all or most locations for which radiation fields are known to exist, and in which workers can be present. Such instrumentation, which can be equipped to alarm and/or record, will monitor for different types of radiation (*i.e.*, alpha/beta particulate radiation, gamma/x-ray electromagnetic radiation, and neutron particulate radiation) and can provide information on the spatial and temporal radiation fields in which a worker can be exposed.

Also important to monitoring the radiation environment is the use of air samplers. These devices can come in many different designs and configurations (Section 5). Most commonly employed in a plutonium facility are static filter samplers, which are often placed so that they sample the air in or near the breathing zone of a worker who is performing tasks with plutonium, such as in a glovebox. It is not unusual for a facility such as a plutonium processing plant to use hundreds of these static air samplers. Under routine conditions, the filters are changed on a schedule and measured

for plutonium content. When the measurements of radioactivity on workplace air filter samples are nonzero, they can provide data useful in reconstructing worker exposures. However, because they typically do not alarm from deposited plutonium, they are only capable of providing a general idea of when a release of plutonium into the work environment may have occurred. On the other hand, the use of alarming continuous air monitors can provide real-time notification of a plutonium release to the work atmosphere. Other radiation protection practices (*e.g.*, wipe surveys of equipment, gloveboxes) also can monitor for the effectiveness of the radiation safety program, bearing in mind that the survey area for RNP may need to be extended due to the increased diffusional mobility of the aerosols.

Equally if not more important than the workplace monitoring data are the measurements obtained from individual workers. For external radiation monitoring, workers will most often wear passive radiation dosimeters as a measure of whole-body absorbed dose, which is converted algorithmically to equivalent and effective dose. In a plutonium processing plant where there is a risk of exposure to neutrons, the dosimeters can contain elements that are sensitive to either neutrons or photons; the neutron detector elements also can be designed to yield information on the energy spectrum of the incident neutrons, which is useful for parameterizing the radiation weighting factor. Other specialized dosimeters can also be employed, such as electronic personnel detectors, which alarm once a selected dose threshold has been exceeded. For tasks in which nonuniform radiation doses are likely (*e.g.*, high doses to hands and extremities), wrist and finger dosimeters also are employed.

Significant attention is usually paid to monitoring for potential inhalation exposures. In terms of PPE and procedures, it is common to require the use of respiratory protection for activities in which there is a risk of release of radionuclide to the atmosphere. Some programs use personal air samplers on at-risk workers to monitor potential exposure (*e.g.*, to plutonium). The use of personal air samplers has been shown to be valuable in identifying individuals who may have been exposed by inhalation (ICRP, 2014). For situations involving high specific-activity materials such as ^{238}Pu, airborne radioactivity concentrations of concern may involve very low PNCs (Appendix C.9). Personal air samplers sampling rates, therefore, need to be high enough to ensure that results are statistically reliable (Scott and Fencl, 1999; Scott *et al.*, 1997).

Nasal swab analysis also is used in some radiation protection programs to monitor for potential inhalation intakes. The swabs can be used to confirm the lack of inhalation intakes for all workers using respirators, or used as a semi-quantitative measure of intake

in cases of known release of radionuclides (Guilmette *et al*., 2007) for normal occupational aerosols. Whether intake estimation would be valid for RNP has not been studied, however.

Bioassay monitoring in plutonium facilities typically consists of a combination of *in vivo* monitoring using detectors specialized to detect the weakly penetrating photons emitted by plutonium isotopes, and urine bioassay. The frequency of monitoring is selected to optimize sensitivity for measuring small undiscovered intakes and depends in part on the models and statistical approaches used for data analysis. When accidental intakes occur or are suspected, then bioassay frequencies (*in vivo* and *in vitro*) are increased to provide better data for assessing the intakes and doses.

When accidents occur in the workplace, information is needed as soon as possible regarding the extent and magnitude of plutonium intakes so that medical managers can assess how they need to manage the consequences of the exposures, including the need for decorporation therapy (NCRP, 2009b). For plutonium intake in wounds, extensive use of localized wound monitoring with collimated detectors is made. For inhalation intakes, there are several useful sources of information, some providing more quantitative data than others. Air concentration data, particularly from continuous air monitors in the vicinity of a release, can be used to calculate time-integrated inhalation exposure, which can be used as a preliminary estimated worker exposure. Nasal swab measurements, which can be obtained in <1 h, can be used to estimate plutonium intakes (Guilmette *et al*., 2007). Less quantitative but indicative of potential inhalation intake include measurements of contamination of the face or exposed skin. All these workplace indicators will trigger the collection of additional bioassay samples, including *in vivo* counts, urine and sometimes feces samples (NCRP, 2009b).

The second part of assessing doses from occupational intakes involves the selection or development of biokinetic/dosimetric models that pertain to the radionuclides and routes of exposure for the workplace, in this case a plutonium processing facility, and the statistical approaches needed to apply the models and associated parameters to the available bioassay and exposure data. The models and how they relate to handling the unique characteristics of RNP have been described in Section 5 and will not be treated further here. The statistical procedures however merit some additional discussion.

As described by ICRP (2015), there are two basic approaches used in retrospective dose assessment for intakes of radionuclides: (1) calculation of intake based on direct (*in vivo*) or indirect (*in vitro*) bioassay measurements followed by calculation of committed

effective dose (CED); or (2) calculation of CED directly from the measurement data using functions that relate them to the time of intake. The first case is the approach presently used by the vast majority of dose assessors, mainly because the second approach is a relatively recent concept and the coefficients needed to calculate CED directly from measurement data have yet to be published, although the principles for calculating them are known (Berkovski *et al.*, 2003).

Calculating intakes based on bioassay data can be done relatively simply for single measurements, but becomes complicated rapidly when multiple data analysis is desired or required. For a single measurement, the intake activity, I in becquerel, can be derived from the measurement value, M in becquerel, using the unitless intake retention function, $m(t)$, as:

$$I = \frac{M}{m(t)} \tag{7.1}$$

The unitless, time-dependent magnitude of the intake retention function represents the time-related whole-body or organ content of the radionuclide (as a fraction of the intake) or the urine or fecal excretion rate of the radionuclide (fraction of intake per day). The fraction of intake values and fraction of intake per day values are obtained using the ICRP models described in Sections 5 and 6. These "forward calculations" are done as a function of time assuming, for example for inhalation exposure, a specific particle size and absorption type (F, M, S). The calculated results are often summarized in tables, which allow the intakes to be derived in a straightforward manner. Some tabulations have been published (Potter, 2002). However, as is always the case, the accuracy of the calculations will depend on the validity of the assumptions about the exposure material (physical size, solubility, chemical form), the attributes of the exposed individual (gender, age, size, activity level during exposure, state of health), and knowledge about the exposure (when and how long it occurred).

For known exposure incidents, it is typical that multiple bioassay measurements will be made, and therefore would be used to assess the intake. Additionally when an incident happens to an employee who has been on a routine bioassay program, then all of their data can also be analyzed together. This is particularly important if the employee has had past exposures, which could affect the interpretation of the most recent bioassay data.

There are numerous statistical methods that can be used for estimating intakes and doses based on multiple measurement data. The International Atomic Energy Agency (IAEA, 2004) has summarized several of these approaches, which include:

- point estimates in which the measurement data are treated independently as described above to yield a population of intake estimates, which are then treated statistically;
- unweighted least squares fitting;
- weighted least squares fitting in which the weighting is based on knowledge of the variability/uncertainty in the measurement data;
- maximum likelihood or χ-squared methods; and
- Bayesian statistical inference techniques.

The selection of analytical technique can depend on the user's knowledge of statistical variability of the bioassay and exposure data (*e.g.*, normal or lognormal variance), the magnitude of exposure (larger exposures merit greater analytical effort and presumably result in more accurate dose estimates), the knowledge and skills of the assessor, and the availability of statistical software to perform the somewhat complex calculations.

In any case, the more complex the statistical methods envisioned, the greater the need to consider uncertainties in the measurement data, understanding of the exposure scenario, route of intake, radionuclide composition, particle size if for inhalation, biokinetic/dosimetric model structure, and parameter values. NCRP (2009e) has provided detailed analysis of methods for identifying and quantifying uncertainties in all the above factors for internally deposited radionuclides, and can be used effectively in designing a radiation dose assessment program. ICRP (2015) makes effective use of the information in NCRP Report No. 164 (NCRP, 2009e).

7.3 Impact of Radioactive Nanoparticles on Dose Assessment

The impact of exposure to RNP on dose assessment can be viewed from two perspectives, dose assessment methods and techniques, and the magnitude of the dose assessment. The first relates to relevance and uncertainties in dose assessment methods, the second to the relationship between bioassay and exposure measurement data and the resulting calculated doses.

In general the presence or absence of RNP in an exposure environment will have little effect on the choice of method appropriate for dose assessment, which are outlined in NCRP Report No. 163 (NCRP, 2009d). Defining exposure scenarios, identifying exposure pathways, developing dose assessment methods, evaluating uncertainties, and communicating results to stakeholders are processes that are relatively insensitive to RNP characteristics such as particle size, shape and solubility. Nevertheless, as pointed out in Section 5 on operational health physics, there are considerations for

radiation protection program planning that may ultimately impact dose assessment methods (*e.g.*, in terms of bioassay monitoring; sampling frequencies; air-sampling instrumentation, placement and use; and use of PPE). For example, a monitoring program that relies heavily on the use of personal area samplers may need to account for particle size-specific differences in collection efficiencies for RNP in order to better correlate measured activity on the filter with exposure probability and intake estimation, although the latter is not recommended (ICRP, 2014). This may also be the case with nasal swab methods, since no analyses have been done involving RNP particle sizes. On the other hand, the results of radioactivity counting of urine and fecal samples and of *in vivo* monitoring would not be significantly influenced by considerations of particle size, including the presence of RNP.

The impact of RNP on dose assessment principally will be due to their effects on the relationship between measured bioassay data and the doses that are ultimately calculated. Although the extent to which RNP can affect exposure-dose relationships has yet to be studied in detail, it is reasonable to speculate that RNP effects on biokinetics, particularly for inhalation and wound intakes, will affect the exposure-dose relationships calculated based on bioassay data. It was pointed out in Section 6 that there are several aspects of biokinetics that may be unique to RNP, such as regional deposition in the respiratory tract; availability of RNP to be absorbed to blood; and fate of RNP that reach the blood. Thus if the spatial and temporal radiation dose patterns are shown to depend on RNP characteristics, then these differences likely will affect the exposure-intake-dose relationships. So whether a dose assessment is done using the traditional intake estimation or the more recent dose per unit measurement method, the relationships will change. Presently there are insufficient examples of dose assessment modeling of radionuclides with various routes of exposure to determine whether the magnitude of uncertainties in dose assessment is small or large.

As an example evaluation of the impact of RNP properties on bioassay interpretation, Cash (2014) and Cash *et al*. (2016) examined the results of several experimental studies (Smith *et al*., 1977; Stradling *et al*., 1978a) in which rats were exposed by inhalation or intratracheal instillation to ^{239}Pu or ^{238}Pu oxide NP. In studying the biokinetics in control and diethylenetriamine pentaacetic acid (DTPA)-treated animals, the original study authors noted that the plutonium NP were significantly more soluble *in vivo* than were the particles with larger particle sizes. Cash (2014) and Cash *et al*. (2016) showed that using ICRP HRTM default parameters in the

micrometer-size range for PuO_2 to predict biokinetic behavior of PuO_2 following inhalation of plutonium NP of AMAD 10 and 250 nm would underpredict the urinary excretion of plutonium (Figure 7.1). For ^{239}Pu material of AMAD 10 and 250 nm, a higher urinary excretion of plutonium is likely to occur compared to excretion associated with Type S material of the default occupationally relevant particle size of 5 μm.

It is possible that the increase in urinary excretion of the nano-sized particles compared to the default 5 μm diameter particles may be due to the increase in dissolution rate that could result from the greater surface area-to-mass ratio of the smaller particles. As shown in Figure 7.1, the assignment of higher material-specific solubility parameters could be made in the HRTM model to account for the increased dissolution rates of the NP. The daily urinary excretion activity values for NP with an AMAD of 10 nm are about two orders of magnitude higher than those for a typical 5 μm Type S material. These conclusions assume that the biokinetic behaviors noted in the previously described rat studies are predictive of biokinetics in humans exposed to similarly produced plutonium aerosols and having similar particle size distributions.

Interpretation of bioassay measurements from individuals exposed to PuO_2 NP with the assumption that the biokinetic behavior of PuO_2 NP is the same as that of micrometer-sized plutonium particle parameters can result in an over prediction of the CED by two orders of magnitude. Consequently intakes and CED could be overestimated from bioassay measurements if the materials contained in the exposure were known to be in the NP size range and Type S absorption parameters were assumed (Figure 7.2). In addition, if air measurements are used for interpretation, the CED for an inhalation intake of ^{239}Pu NP is higher than that of an intake of ^{239}Pu materials of 5 μm AMAD and Type S behavior. However a smaller CED will be calculated when the dose assessment is performed based on urinary excretion measurements. The authors note that although in this case the use of the default assumptions (5 μm AMAD, Type S) for assessing dose following inhalation exposure to airborne PuO_2 NP appears to be conservative, the evaluation of situations involving PuO_2 NP that may have different particle size and solubility properties should prudently follow the ICRP recommendation to obtain and use additional, material-specific information whenever possible.

It should be noted again, however, that the results and conclusions of Cash (2014) and Cash *et al*. (2016) were based on a single set of experiments in which plutonium aerosols were produced using one method (*i.e*., exploding foils). There have been other studies

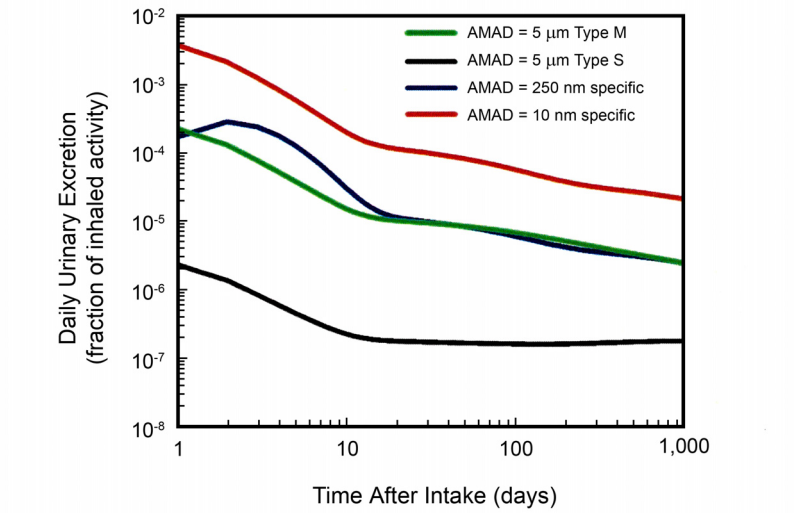


Fig. 7.1. Comparison of calculated daily ^{239}Pu urinary excretion rates in humans based on default particle size and blood absorption parameters to rates based on material-specific solubility parameters derived from plutonium NP studies (Cash, 2014; Cash *et al*., 2016).

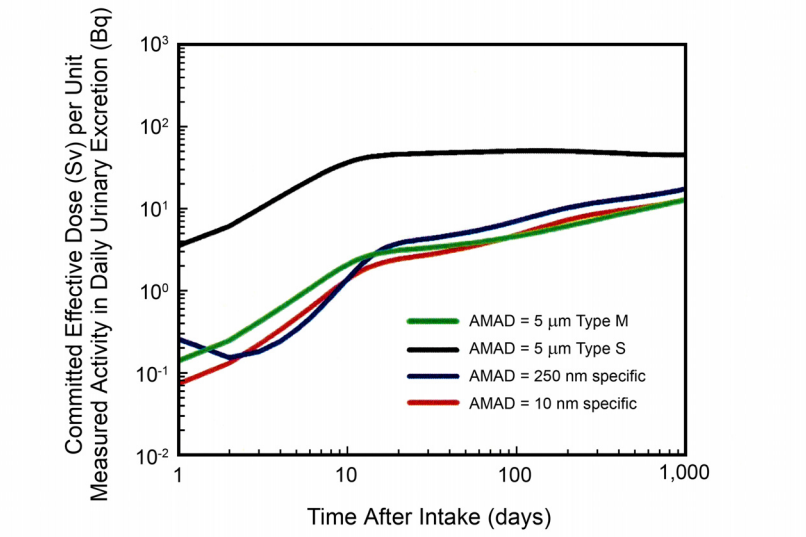


Fig. 7.2. Comparison of the calculated committed effective dose in humans per unit measured activity in daily urinary excretion for inhaled ^{239}Pu based on default particle size and blood absorption parameters to calculated dose coefficients based on material-specific solubility parameters derived from plutonium NP studies (Cash, 2014; Cash *et al*., 2016).

conducted in which plutonium NP were produced using other techniques where their solubility was very low. For example, Kanapilly and Diel (1980) produced plutonium oxide particles of low solubility by heat treating a nebulized plutonium diketonate chelate complex. In any case, it is clear that additional research is needed to sort out the dose assessment uncertainties that might be attributed to RNP.

7.4 Impact of Radioactive Nanoparticles on Medical Management Decisions

The challenge for medical professionals who receive patients exposed to radiation is to medically manage those persons such that the extent and magnitude of health effects occurring either early after the contamination event (tissue reactions) or later in life (cancer, cardiac, genetic risks) is minimized. For external radiation exposure, information on whole-body dose obtained from personal dosimeters, scenario reconstruction, or biodosimetric endpoints can provide early guidance to the practitioner. However, in the absence of knowledge of the exposure doses, the patients will be managed based on measured clinical endpoints (such as evidence of prodromal symptoms, hematologic and clinical chemistry, infection, and biomarkers of radiation effects). The presence of RNP in sufficient quantities that would produce large radiation fields would not be expected to result in conditions that would affect how such external radiation situations would be managed as long as the characteristics of the penetrating radiation are understood. However, the situation for triaging and managing the consequences of intakes of radionuclides is more complicated.

There is an important difference between external and internal exposures in terms of how radiation dose is delivered. For external radiation, exposure and delivery of dose to the organism are completely correlated (*i.e.*, when the exposure occurs, dose is delivered, when the exposure ends, the dose has been delivered). Thus, from the medical perspective, consequence management for external exposures deals with treating patients who have already received their radiation dose.

For intakes of radionuclides, the relationship between exposure and dose delivery is less temporally linked because in most cases, the dose is acquired with time beginning with the exposure, but often continuing for long times after the intake has ended. For example, Table 7.1 illustrates the differences in how radiation dose is distributed in time for a variety of radionuclides with different physical and biological half-times. Expressed as a fraction of the CED, which is integrated over a 50 y period for occupational exposures, for ^{131}I (8.0 d physical half-time), 94 % of the CED is delivered

TABLE 7.1—*Fraction of 50 y cumulative effective dose for radionuclides inhaled occupationally (5 μm AMAD, single exposure) (NCRP, 2009b).*

Time Post Exposure (d)	Radionuclide (absorption type) (fraction 50 y CED)			
	^{131}I (F)	^{137}Cs (F)	^{238}U (M)	^{239}Pu (M)
1	0.062	0.025	0.036	0.0028
7	0.47	0.074	0.18	0.014
30	0.94	0.20	0.51	0.041
365	1.00	0.90	0.90	0.095
1,826 (5 y)	1.00	1.00	0.94	0.21
7,305 (20 y)	1.00	1.00	0.96	0.54

in one month. Cesium-137, with a 30 y physical half-time, but relatively short biological retention (~90 d) delivers 90 % CED in 1 y, all of the dose by 5 y. For radionuclides like ^{238}U and ^{239}Pu, which have very long physical half-times as well as long-term biological retention, radiation dose is delivered over the entire 50 y period. For ^{239}Pu, only half of the CED is delivered in 20 y.

Thus, the fact that dose is delivered over a protracted period can be a source of considerable concern for the patient and is a challenge for risk communication. On the other hand, the protracted dose delivery may result in lower risk due to cell and tissue repair mechanisms, as well as offer an opportunity in consequence management if the clearance of the radionuclide from the body can be accelerated by chemical or physical intervention (decorporation therapy). NCRP Report No. 161 (NCRP, 2009b) extensively describes the approaches and methods for managing persons contaminated with radionuclides.

As part of its comprehensive treatment of protocols for assessing and treating radionuclide-contaminated individuals, NCRP Report No. 161 (NCRP, 2009b) defined an operational quantity, the Clinical Decision Guide (CDG), to aide practitioners in making decisions about treatment of the contaminated persons. The CDG is designed to trigger treatment based on a combination of three dose endpoints: (1) intakes of radionuclides (excepting radioiodine) that would result in a 250 mSv CED (1.3 % lifetime risk of fatal cancer attributable to radiation); (2) a 30 d RBE-weighted absorbed dose of 0.25 Gy-Eq (based on tissue reactions to bone marrow); and (3) a 30 d RBE-weighted absorbed dose of 1 Gy (tissue reactions to lung). To facilitate application of the CDG in the clinical environment, NCRP Report No. 161 (NCRP, 2009b) calculated intakes,

in vivo measurement quantities, urinary excretion levels and nasal swab activity levels (for inhalation) for the most probable set of radionuclides to which people could be exposed and for different routes of intake (inhalation, ingestion, intravenous injection) to allow the medical practitioner to link available bioassay data to the CDG. The report also elaborates on radioelement-specific decorporation strategies and provides information on implementation.

So how would the presence of RNP in an exposure affect the process of medical management of persons contaminated with radionuclides? Based on the information available and the points raised in this Report, it is not clear what the impacts might be. The CDG values for various radionuclides are not likely to change because of the presence of RNP as the criteria for calculations are based on radiobiological endpoints that are derived mostly from the effects of external radiation. However, the calculation of the tabulated bioassay quantities for individual radionuclides is based on the application of existing biokinetic models, particularly those of ICRP. To the extent that RNP affect the structure or parameterization of those models, as discussed in Sections 5 and 6, then these uncertainties will propagate into the CDG calculations, and may modify the trigger levels for bioassay. As stated before, more research and investigation is needed to evaluate the magnitude of the uncertainties that could be introduced by different RNP biokinetics as well as whether other compartmental modeling strategies need to be considered.

8. Conclusions and Recommendations

The majority of the elements of a standard radiation safety program for handling radioactive materials are directly applicable to the handling of radioactive nanomaterials or are applicable with minor modifications in situations where potential exists for dispersion of RNP. The program element that could potentially require the most modification is internal dosimetry. It is believed the current models for performing internal dose calculations will be suitable; however, the possible differences in the biokinetics of RNP may require the adjustment of uptake, transfer and elimination parameters when performing internal dose assessments.

The specific conclusions and recommendations from this Report are summarized below.

8.1 Hazard and Exposure Assessment

8.1.1 *Conclusions*

As discussed in Section 3, the conclusions for hazard and exposure assessment include:

- The hazards and pathobiological properties of RNP may not only be comprised of the radiological hazards but also by their chemotoxic and nanotoxic hazards. The nature of the combined hazards may result in additive or synergistic effects, depending on the radionuclide involved as well as its specific activity within the RNP.
- At aerosol concentrations $>10^7$ particles per centimeter of air, the ongoing coagulation under the typical thermodynamic conditions of atmospheric aerosols does not allow the formation of a stable aerosol of NP for more than a few seconds (Hinds, 1999). This is due to rapid coagulation, which leads to a shift in size distribution towards increasing NP sizes at the same time that their number concentration is rapidly decreasing.
- Unique features of exposure to NP aerosols are their low mass but high number concentrations and high surface area per unit mass or volume.

- Limiting the dose and exposure metrics to only mass concentration data for the NP portion of an aerosol may not be sufficient for a complete description/characterization of RNP.
- Limiting inhalation exposures to RNP by radioactivity concentration should result in particle mass concentrations well below any occupational exposure limits currently recommended for NP.
- NP deposition is mainly determined by their diffusion properties. However, large agglomerates of a few hundred nanometers consisting of aggregated or agglomerated primary particles may well deposit due to their settling and impaction properties. Hence, deposition of RNP < 100 nm in a given airway or in the alveoli is rather uniform over the respective entire surface areas. Thus, in a given airway generation and in the alveoli, RNP deposit by diffusion, which results in a rather uniform deposition pattern. For different airway generations, differences in deposition patterns exist.

8.1.2 *Recommendations*

Dose metrics of RNP need to consider including not only the mass concentrations of the aerosol distribution but also the number and surface area concentrations of the aerosol distribution. The relative importance and toxicological implications of the respective dose metrics likely will depend on the nature and quantity of the radionuclide and the NP.

8.2 Operational Health Physics

8.2.1 *Conclusions*

As discussed in Section 4 and summarized in Table 4.1, most of the elements of a standard radiation safety program for handling radioactive material are directly applicable, or are applicable with minor modification, to handling radioactive nanomaterials.

Specifically, the radiation safety program elements that are generally directly applicable to handling radioactive nanomaterials include:

- ALARA principle;
- external dosimetry program;
- evaluation of potential chemical and physical hazards;
- engineered controls:
  - use of gloveboxes and hoods for handling dispersible material;
  - exhaust ventilation and HEPA filtration;

  - access control systems (such as warning signs, warning lights, audible signals, and physical barriers); and
  - shielding.
- administrative controls:
  - standard (basic) radiation safety training;
  - safety procedures;
  - labeling requirements; and
  - posting requirements.
- PPE; and
- radiation monitoring:
  - external radiation surveys;
  - air sampling; and
  - contamination surveys.

However, because of the potential dispersibility of nanomaterials, additional considerations apply to some of the elements of a standard radiation safety program. They include:

- The ventilation currently used to control exposures to gases, vapors, and airborne particles in general is sufficient to control exposures to RNP. New laboratory hoods based on low-flow and/or low-turbulence enclosures reduce the inadvertent loss of material during the handling of NP powders. The ventilation rates for gloveboxes and hoods should be properly adjusted to minimize the potential for the spread of contamination both inside and outside of these enclosures (Section 5.2.3).
- The RPE currently available to control exposures to gases, vapors, and airborne particles in general is sufficient to control exposures to RNP. Careful attention should be given to properly maintaining and fitting respirators, as leakage past face and respirator cartridge seals is a concern for particles of all sizes, especially those near the most-penetrating-particle size for respirator media.
- There is an increased possibility that nanomaterials may penetrate anti-contamination clothing that is made of woven fabric material.
- Contamination control programs should consider the potential for wider contamination spread when dispersible materials are being handled.
- In addition to standard radiation safety training requirements, training should include any unique characteristics and safety considerations related to radioactive nanomaterials.

The elements of the radiation safety program that may require significant modification when handling nanomaterials include:

- particle size analysis of airborne nanomaterials requires sophisticated equipment and special expertise (Section 5.2.3.4); and
- the potential differences in deposition, translocation and elimination from the body following intakes should be carefully evaluated as they relate to internal dose determinations (Section 6).

8.2.2 *Recommendations*

It is recommended that:

- for RNP the guidance on LEV for radioactive materials be read in conjunction with that for nanomaterials in determining the appropriate type of LEV (Section 5.2.2.2).
- where unsealed highly radiotoxic material or radioactive materials in a dispersible form are used (including in nanoform) HEPA filters be used to filter local containment system exhausts (Section 5.2.3.4).
- the measurement of aerosol particle size be conducted by specialists with expertise in the use of the specialized equipment required (Section 5.2.3.4.).
- in workplaces with potential exposure to nanomaterials, clothing made from low dust-retention and -release fabrics, such as polyethylene textiles, be used (Section 5.2.4.1.3).
- the full range of applicable regulatory requirements be considered when determining appropriate waste management approaches to radioactive nanomaterials (Section 5.4).
- attention be paid to nanotechnology and radiation-related risk perception and risk communication for workers and the community (Section 5.8).

8.3 Nanoparticle Issues for Radiation Dosimetry

8.3.1 *Conclusions*

The impact of exposure to RNP versus other sized radioactive materials has been considered from the viewpoints of (1) route of intake (*i.e.*, inhalation, ingestion, wound, dermal); (2) biokinetic behavior in the intake tissues and organs — as well as the systemic organs—after reaching the blood; and (3) the selection and description of target organs and tissues for calculating doses. Accordingly, the following can be concluded based on present knowledge of RNP and current biokinetic/dosimetric models:

- For ingestion intake of RNP, the ICRP (2006a) HATM appears to provide an adequate biokinetic and dosimetric model in that particle size is not considered an important factor influencing the distribution of radionuclides within the HAT contents or the absorption to blood. Nevertheless, studies with ingested engineered nanomaterials have shown that transluminal transfer of particles, at least to liver, can occur, and may add a complexity to the biokinetics not observed with larger particles.
- For intakes *via* RNP-contaminated wounds, the NCRP (2006) wound biokinetic model appears to be adequate in structure and parameterization to accommodate the unique features of RNP for both biokinetics and dosimetry, although it is recognized that new parameter values may be required to better describe RNP biokinetics.
- For inhalation exposures, although there are very good models by ICRP (1994a) and NCRP (1997) for describing the biokinetics and dosimetry of inhalation intakes of radionuclides, there are aspects of the models as they are currently configured that need to be considered in order to describe some of the unique features of inhaled RNP. Specifically:
  - The experimental data available describing the total deposition of various sized aerosol particles in the human respiratory tract are adequate to encompass the range of sizes of RNP, and can be considered directly applicable for modeling purposes.
  - The data available describing the regional deposition of different sized aerosols in the human respiratory tract are not adequate. This lack of knowledge, particularly for nanometer-sized particles, leads to significant uncertainty about where in the respiratory tract the particles will deposit.
  - Probably the most consequential uncertainty relates to the regional deposition of RNP in bronchi. This is reflected by the more than twofold differences in predicted deposition fractions in the bronchi and in the pulmonary region for the ICRP and NCRP models. Since this uncertainty often will be propagated into uncertainty in dose coefficients of similar magnitude, additional research would be welcome.
  - The recognized differences in rates and amounts of phagocytosis of RNP by airway and alveolar macrophages versus larger particles result in different distribution and retention patterns in the respiratory tract,

but particularly in the parenchymal region of the lung. Thus, the fate of RNP within the lung microstructure can be different from that of micrometer-sized particles, and lead to biokinetic/dose distributions that are different and presently not accounted for by present models.
  - Because of the differences in microscopic distribution of NP versus larger particles in the lung, it is not clear whether the current HRTM is adequate. The microdosimetric aspects of exposures to RNP will depend on the location of deposition, the type and energy of radioactivity and the rate of removal.
  - An expanded HRTM that takes into account the clearance of intact RNP to additional target tissues appears to be necessary. For example, additional transport rates for intact RNP are proposed between each of the lung compartments in the current HRTM and blood. Also, translocation *via* neurons from the upper respiratory tract and tracheobronchial region to the CNS can be accounted for, along with translocation from the respiratory tract to the CNS *via* vagal nerve structures (Section 6.5.2).
- It is clear from experimental data that the rate of translocation, tissue distribution, and retention of RNP that reach the blood differs substantially from those for solubilized radionuclides. These differences presently cannot be taken into account by current systemic biokinetic models and likely will require new approaches for modeling.

8.3.2 *Recommendations*

It is recommended that:

- in dosimetric models, chemical and particulate dosimetry quantities and factors may need to be evaluated in addition to the more traditional radiological dosimetry quantities. In addition, the possibility that biological effects may occur as a result of combined insults from the radiological, chemical and particulate properties of RNP should be investigated.
- new transport pathways and rates for NP translocation across the ABB be considered for inclusion in a new HRTM (Section 6.5.2).
- the modeling of the systemic biokinetic behavior of RNP reaching the blood be treated discretely from solubilized radionuclides in blood because the uptake, distribution and retention of particulate and soluble radionuclides systemically are very different (Section 6.5.2).

- for chronic exposure conditions the additional accumulation of poorly soluble NP in secondary organs (an important issue) be addressed in future reports (Section 6.5.2).

8.4 Dose Assessment and Medical Management

8.4.1 *Conclusions*

The impact of exposure to RNP on dose assessment depends on the perspective being considered. In terms of methods and techniques of dose assessment, there appears to be little reason to believe that current methodologies, such as those outlined in NCRP Report No. 163 (NCRP, 2009d), would not be appropriate in dealing with dose assessment exposures involving RNP. This would include defining exposure scenarios, identifying exposure pathways, developing dose assessment methods, evaluating uncertainties, and communicating results to stakeholders.

On the other hand, the same cannot be said for the impact of RNP on dose assessments themselves. Because of the possible influences of RNP on the structures and parameters of the various biokinetic/dosimetric models, it can be expected that quantitative relationships between bioassay measurements, intake estimation, and ultimately dose estimation will be modified by the presence of RNP, for the reasons described in Section 6. The effects of RNP exposure on these bioassay-intake-dose relationships have not been studied at the present time. Therefore, it is not possible to predict whether the uncertainties would result in conservative versus nonconservative estimates relative to not accounting for such RNP effects. There is clearly a need to address these potential uncertainties.

The possible effects of RNP exposure on medical management decisions are not clear at this time because the effects of RNP exposure on bioassay-intake-dose assessment have not been adequately evaluated. Using the operational quantity for medical management decision making developed in NCRP Report No. 161 (NCRP, 2009b) (*i.e.*, the CDG), RNP exposure would not be expected to change the values of the stochastic effects and tissue reactions triggers for the CDG, as those are based on radiobiological endpoints derived from the effects of medical exposures. If there are to be effects on CDG from RNP exposure, they will be due to the altered relationships between bioassay quantities, intake and dose estimation, as was the case in dose assessment. Thus, these dose assessment uncertainties may lead to modifications in the trigger levels for bioassay.

8.4.2 *Recommendations*

It is recommended that more research and investigation of the material-specific characteristics and biokinetic behavior of RNP be undertaken to evaluate and reduce the magnitude of the current uncertainties in dose assessment models (Section 7.2).

Appendix A

Radiolabeled Nanoparticles

A.1 Use of Radionuclides to Characterize and Quantitate Nanoparticle Contents

In recent years, many applications of NP and their aerosols have been used in which radionuclides provided easy-to-detect labels to characterize and quantitate NP contents and identify the specific chemical elements in those NP. One approach has been to radiolabel the NP prior to their use in toxicology or environmental studies and then to determine the radioactivity content of the exposed laboratory animals' organ and tissue samples or environmental samples as a measure of the presence of the NP in those samples. Another approach has been to perform retrograde irradiation either by neutrons or by accelerated ions in order to cause a nuclear reaction of selected chemical elements of interest resulting in radionuclides which were subsequently quantitated by radiation spectroscopy. For example, in an environmental study of diesel soot in the mid-1980s (Horvath *et al*., 1987), the total amount of diesel fuel sold at all fueling stations in Vienna and the surrounding vicinity over a four-week period was labeled using an organic complex of the nonradioactive metal dysprosium. Air samples were then collected throughout the city and the airborne mass of soot NP was estimated by neutron activation of the dysprosium. From the measured ^{166}Dy content of the air samples, the authors found a clear correlation between the mass concentration of diesel soot emission and traffic density of diesel powered cars.

A.2 Radiolabeled Nanoparticles for Biokinetic and Toxicologic Investigations

Biokinetics and toxicological studies using radioactive particles or radiolabeled particles either as aerosols or as particle suspensions

have a long tradition (ICRP, 1994a) since the radiolabels allowed determination of the fate of the radiolabeled particles by rather simple radioanalysis measurements. These measurements usually provided only an overview of the biokinetic fate within the body but did not give detailed insight on the particles' retention at a microscopic level. This technology was further developed and adapted to radiolabeled NP and there have been numerous reports published over the last two decades. Many of these reports use short-lived radionuclides (such as ^{99m}Tc, ^{111}In, and ^{131}I) for convenience to enable the research to be conducted within radiation protection standards. Yet a radionuclide which is not an integral part of the chemical compound in the particle matrix may be leached from the particle and since radioactivity measurements cannot distinguish between the radiolabel inside the original particle or a metabolic compound after leaching, the challenge was to firmly fix the radiolabel within the particle matrix which itself needs to be virtually insoluble in the fluids of the organism. The best way to achieve firm fixation was to use a radionuclide that was chemically part of the NP compound. Therefore, meaningful biokinetics and toxicological studies require extensive investigations on the stability of NP and their radiolabels. Note that simple *in vitro* testing in aqueous dispersion solvents on the dissolution and degradation of the NP and its radiolabel is usually only a first step in those investigations and needs to be followed by additional *in vivo* dissolution and degradation studies.

A number of studies on the generation and characterization of RNP and resulting physical and chemical properties are given in Table A.1. Furthermore, studies which focus only on the organ(s) of interest in which usually less than half of the administered radiolabeled particle dose is retained raise many questions, often unresolved, on the disposition of the rest of the administered material and the radiolabel including dissolution and/or degradation and metabolization of both. One option is the quantitative radioanalysis over time of the biodistribution of not only all organs and tissues of interest but also including the remaining carcass and total excretion. This provides better insight regarding the metabolic fate of the administered NP and its radiolabel. Appendix B, Table B.1 provides a list of published biokinetic and toxicological studies obtained after the administration of RNP.

Studies examining these issues have been conducted at the Joint Research Center, Ispra, Italy (Abbas *et al*., 2010; Gibson *et al*., 2011). Additional studies were conducted at the Helmholtz Center, Munich, Germany using a variety of compounds including elemental carbon (EC): ^{99m}Tc-EC (technegas) (Seden *et al*., 1997), ^{111}In, ^{198}Au-Fe_2O_3, ^{192}Ir, EC-^{192}Ir NP, ^{48}V-TiO_2–, and ^{198}Au + ^{195}Au–

TABLE A.1–*Examples of the production of RNPs for studies of their physicochemical properties, generation and characterization.*

Study Type[a]	RNP[b]	Size[c] (nm)	Radionuclide	Radionuclide Source[d]	Reference
PC	MWCNT	—	^{7}Be	Proton beam cyclotron	Abbas *et al.* (2013)
BD	MWCNT	—	^{14}C	—	Czarny *et al.* (2014)
PC	MWCNT	—	^{14}C	—	Larue *et al.* (2012)
GC, PC	Silver NP	7	^{105}Ag	Proton beam cyclotron	Ichedef *et al.* (2013)
PC, GC	TiO_2 anatase	7 to 10	^{48}V	Proton beam cyclotron	Holzwarth *et al.* (2012)
PC, GC	GNP	20	^{198}Au, ^{195}Au	Reactor neutron activation, proton beam cyclotron	Moller *et al.* (2013)
BD	Diblock copolymer NP (encapsulating Propac 7)	—	^{3}H	—	Johnstone *et al.* (2011)
GC, PC	TiO_2, P25 anatase + rutile	25	^{48}V	Proton beam cyclotron	Abbas *et al.* (2010)
GC, PC	TiO_2	—	^{48}V	Proton beam cyclotron	Kreyling *et al.* (2011)
BD	Silver, CeO_2, cobalt NP	—	^{110m}Ag, ^{141}Ce, ^{60}Co	Neutron activation	Oughton *et al.* (2008)

[a]PC = physicochemical properties; GC = generation and characterization; BD = biodistribution
[b]RNP = radioactive nanoparticle; MWCNT = multi-walled carbon nanotube; NP = nanoparticle
[c]Sizes are given for primary particles which usually buildup larger agglomerates/aggregates over time.
[d]Radionuclide sources include production by proton cyclotrons and other accelerators that involve beam interactions with target materials (*i.e.*, nuclear reactions) or by reactors involving neutron activation.

AuNP (Alessandrini *et al*., 2008; Geiser and Kreyling, 2010; Hirn *et al*., 2011; Kreyling *et al*., 2002a; 2002b; 2009; 2011; 2013; Lipka *et al*., 2010; Moller *et al*., 2004; 2006; 2008; Roth and Stahlhofen, 1990; Roth *et al*., 1997; Schleh *et al*., 2012; 2013; Semmler *et al*., 2004; Semmler-Behnke *et al*., 2007; 2008; 2012). Additional studies were conducted at the Commissariat a l'Energie Atomique using ^{14}C MWCNT (Czarny *et al*., 2014; Larue *et al*., 2012). Technetium-99m labeled CNT were studied at the University of London (Singh *et al*., 2006). Another study examined the transport of NP across rat nasal mucosa (Brooking *et al*., 2001). Oughton *et al*. (2008) used ENP with neutron activation of ^{110m}Ag, ^{141}Ce, and ^{60}Co as a tool for tracing ENP environmental fate and uptake in organisms.

Notable experiences relating to ^{99m}Tc EC-NP have been reported in the literature. In those studies a remarkable misinterpretation and its retrograde correction of the biokinetics of inhaled ^{99m}Tc-labeled elemental carbon NP in human subjects originated from a study by Nemmar *et al*. (2002). The freshly generated aerosol of a technegas aerosol generator was inhaled in human subjects and the biokinetics were followed by gamma camera imaging. The authors claimed to have found a rapid uptake of ^{99m}Tc EC-NP in the liver as a result of rapid translocation across the ABB of the human lungs. These findings were published and immediately were cited in many epidemiologic studies on the adverse health effects of ambient ultrafine aerosol particles. Interestingly, Nemmar and co-workers also provided a whole body scan of one of the human subjects which clearly demonstrated the distribution pattern of the ^{99m}Tc pertechnetate molecule in the entire skeleton and thyroid as is well known in nuclear medicine. These initial findings were questioned by numerous research groups which repeated these studies but never could confirm the claimed EC-NP translocation across the ABB (Brown *et al*., 2002; Kreyling *et al*., 2006; Mills *et al*., 2006; Moller *et al*., 2004; 2006; 2008; Nemmar *et al*., 2002; Wiebert *et al*., 2006a; 2006b).

A.3 Radiolabeled Nanoparticles for Diagnostic Medicine

There are several radiopharmaceutical kits available which are based on radioactively labeled diagnostic compounds used in nuclear medicine involving NP. These include kits based on:

- ^{99m}Tc-labeled sulfur-colloids;
- albumin beads radiolabeled with ^{99m}Tc or ^{111}In; and
- liposomes labeled with ^{99m}Tc.

For the past several decades an NP aerosol generator (technegas made up of ^{99m}Tc EC-NP) has been used in nuclear medicine for perfusion and ventilation scans of the lungs and respiratory tract. It is named by the erroneous term "technegas generator" in order to imply the inhaled aerosol is a gas. However, the output of the generator is actually an aerosol of freshly produced carbon NP radiolabeled with ^{99m}Tc, which is produced by following the evaporation-condensation process of a graphite crucible heated up to 2,500 °C containing some desiccated ^{99m}Tc. The aerosol is highly concentrated such that coagulation leads to dynamic shifts in NP size and concentration (Figure A.1). The transmission electron microscope image in Panel A of Figure A.1 shows particles being generated without any ^{99m}Tc eluate loading of the crucible (Moller *et al*., 2006). The aggregated particles are ~100 nm in size, but consist of subunits of 10 nm. This morphology is in agreement with other ultrastructural studies. Panel B shows particles being generated under the standard operating conditions, where the crucible is loaded with 100 µL ^{99m}Tc eluate in physiological saline and desiccated prior to heat up. Many large particles of several 100 nm in size are visible having a cubic structure. The latter are NaCl crystals having carbon particles attached on their outer surface. When the saline concentration of the eluate is reduced by a factor of 10,000, the cuboidal particles are no longer visible and transmission electron microscope

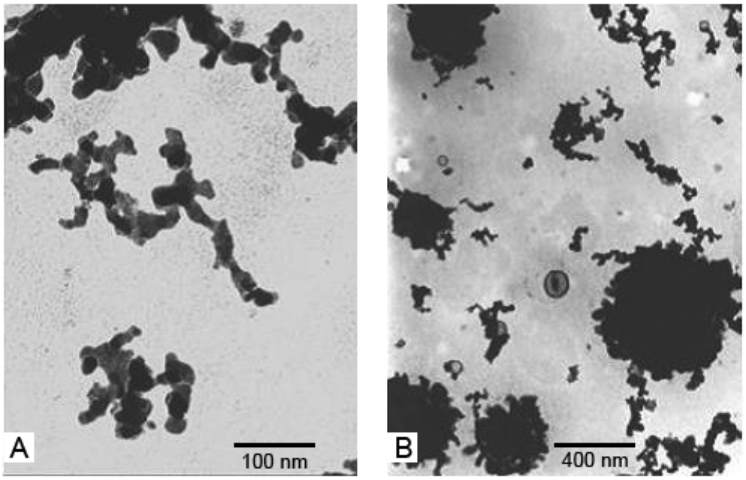


Fig. A.1. Transmission electron micrographs of aggregated/agglomerated technegas particles (Moller *et al*., 2006): (A): Carbon particles being generated without any ^{99m}Tc eluate loading of the crucible. (B): Particles being generated under the standard operating conditions with 100 µL ^{99m}Tc eluate in physiological saline.

images of the carbon particles including ^{99m}Tc show the same morphology as those in Panel A. Unfortunately, in the presence of NaCl crystals the ^{99m}Tc is not only incorporated into the carbon particles but also in the NaCl crystals which immediately dissolve once deposited on the lung epithelium adding a substantial soluble ^{99m}Tc fraction to the inhaled aerosol.

Figure A.2 shows the hygroscopic growth of the inhaled and exhaled aerosol, which was measured by optical photometry at the entrance of the respiratory tract of a human subject. The deposited particle fraction is given as the ratio of the exhaled aerosol over the inhaled aerosol which is, in itself, a function of distilled water dilution of the saline concentration of the ^{99m}Tc eluate in the crucible ranging from dilution ratios of undiluted down to 1:10,000. Also, the carbon aerosol without any eluate in the crucible is given on the left. The "deposition" of the aerosol with undiluted physiological saline shows a negative value since the hygroscopic NaCl particles grew so much in the high relative humidity of the human respiratory. Thus, the exhaled aerosol particles delivered a larger light scattering signal than the inhaled particles. This "negative deposition signal" decreases drastically with increasing dilution of the saline and shows a realistic deposition value for a dilution of 1:10,000 which corresponds exactly to that signal of the carbon aerosol not containing any saline in Moller *et al*. (2006).

Pertechnetate leaching from the carbon/NaCl particles is shown in Figure A.3. Extensive ^{99m}Tc leaching was found for carbon/NaCl particles generated with standard ^{99m}Tc-sodium pertechnetate eluate collected on a filter and trapped within a filter sandwich of 0.025 μm pore size that was suspended in distilled water. In contrast, using a saline free eluate, disappearance of the ^{99m}Tc was much lower. In fact, the authors had some indication that the very small carbon NP penetrated through the sandwich filters (Moller *et al*., 2006).

Figure A.4 compares the whole-body scan of the standard image generated by technegas aerosol (Nemmar *et al*., 2002) in Panel A with a whole-body scan 1 h after inhalation of soluble ^{99m}Tc-sodium pertechnetate with NaCl aerosol particles in Panel B. The latter was obtained by nebulizing a ^{99m}Tc-pertechnetate saline solution with a medical nebulizer. In Panel B, the ^{99m}Tc lung activity had greatly disappeared and accumulation in the bladder, thyroid, and salivary gland (*i.e*., the expected target organs of soluble ^{99m}Tc pertechnetate molecules) was clearly visible. In addition, the visible contour of the body was indicative of the large fraction of ^{99m}Tc activity circulating in the blood. The whole-body scan in Panel A clearly shows the ^{99m}Tc activity in the lungs indicative of substantial ^{99m}Tc-labeled carbon

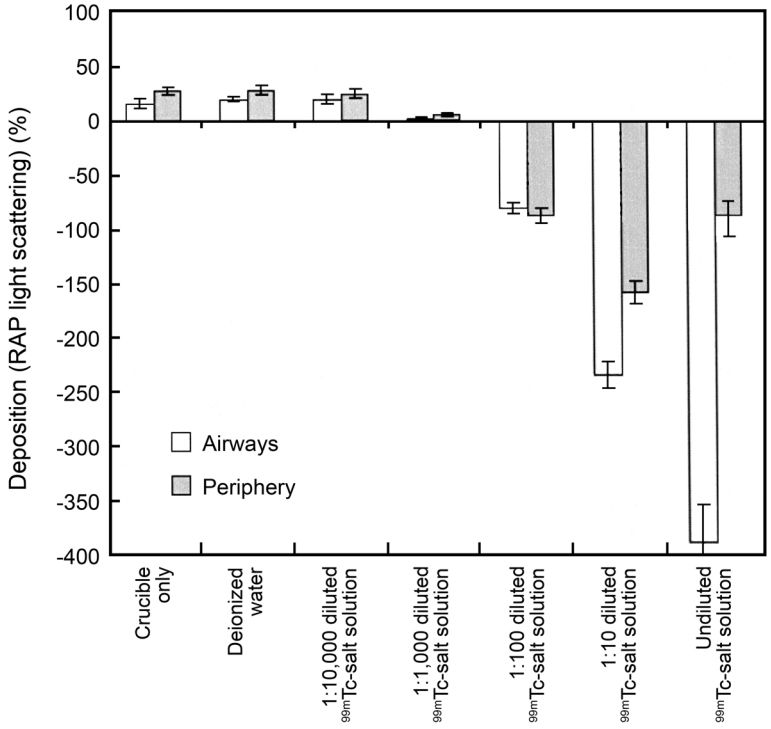


Fig. A.2. Measurement of deposition of 100 nm technegas particles in the human lung by light scattering photometry using the respiratory aerosol probe (RAP) after different generation conditions (Moller *et al*., 2006).

particle retention. However, it also shows similar accumulations in the same organs and the entire body as in Panel B, indicating the results of the metabolism of soluble ^{99m}Tc pertechnetate.

Run properly, the technegas generator produces NP aerosols with sizes <100 nm. When inhaled, the NP deposit in the lungs by diffusion which triggered the name "technegas" associated with the "gas-like" diffusional deposition of the NP. This diffusional behavior can lead to a rather homogeneous deposition pattern in the entire respiratory tract and can be used for perfusion and ventilation diagnostic purposes in patients with lung diseases (Kreyling *et al*., 2006; Moller *et al*., 2004; 2006; 2008; Wiebert *et al*., 2006a; 2006b).

A.4 Radiolabeled Nanoparticles for Medical Imaging

A recent review summarizes novel developments of nuclear medicine in oncology that have involved numerous investigations

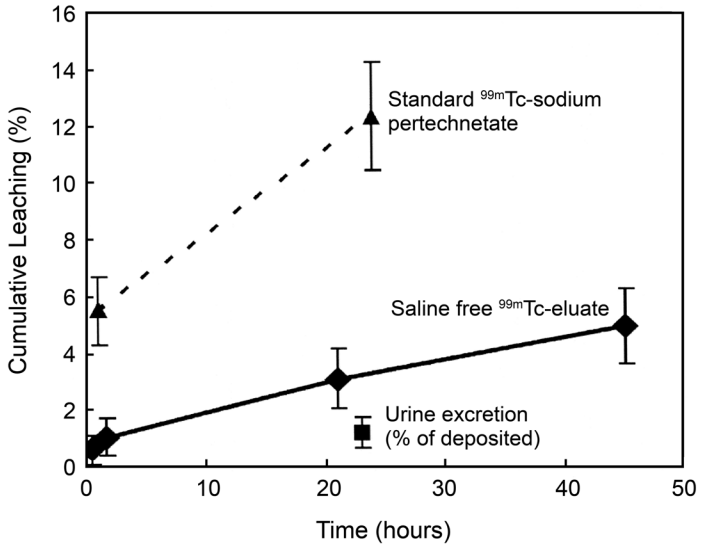


Fig. A.3. Technetium-99m leaching from technegas particles generated with different crucible fillings: standard ^{99m}Tc-sodium pertechnetate (dashed line) and saline-free ^{99m}Tc eluate (solid line). Twenty-four hour cumulative urine excretion after voluntary inhalation is also shown for particles generated with saline-free ^{99m}Tc eluate (Moller *et al*., 2006).

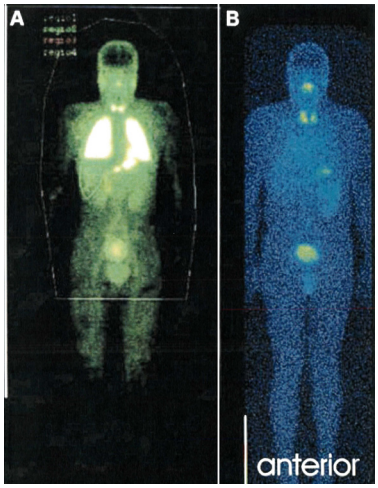


Fig. A.4. (A): whole-body gamma camera scan (anterior) of inhaled ^{99m}Tc technegas (1 h after inhalation) (Nemmar *et al*., 2002). (B): whole-body gamma camera scan (anterior) of inhaled ^{99m}Tc-sodium pertechnetate (1 h after inhalation) and distribution in the body and accumulation in different organs (Kreyling *et al*., 2006).

of novel specific tumor-targeting radiopharmaceuticals as a major area of interest for both cancer imaging and therapy (Hamoudeh *et al*., 2008). Current progress in the pharmaceutical nanotechnology field has exploited the design of tumor-targeting nanoscale and microscale carriers that deliver radionuclides to tissues and cells in a selective manner to improve the outcome of both cancer diagnosis and treatment. These carriers include, amongst others, liposomes, microparticles, NP, micelles, dendrimers, and hydrogels. Often these NP are additionally functionalized with nonradioactive molecules for targeting or other functional purposes to better analyze pathophysiological responses, particularly for the cardiovascular system (Hamoudeh *et al*., 2008; Kumar *et al*., 2010; Merkel *et al*., 2009a; 2009b; Nahrendorf *et al*., 2008). A more recent review of the application of radioactive NP in medical imaging was provided by Kiessling *et al*. (2014).

A.5 Radiolabeled Nanoparticles for Therapeutic Medicine

Currently there are a number of attempts underway to use radioactive NP in therapeutic nanomedicine, predominantly in cancer treatment. Information on selection of NP and radiotherapy isotopes for therapeutic applications, strategies for targeting NP to cancers, and challenges and potential solutions for *in vivo* delivery of NP has been presented in a review by Zhang *et al*. (2010). Chopra (2011) summarized advantages of using NP to deliver therapeutic radioisotopes as follows:

- NP have prolonged blood retention time, ranging from 30 min to 24 h, depending on the morphology and size of the particle, coating materials, and compositions of NP conjugates;
- NP carriers used for targeting cancer cells exhibit high tumor retention time and thus enhance the concentration of therapeutic agents;
- NP have high loading capacity, they can even carry more than one type of radioisotope;
- internalization of receptor targeted NP leads to the uptake of large amounts of radioisotopes into the target cells, resulting in effective killing of tumor cells with a relatively low level of receptor-expression; and
- the unique chemical and physical properties of NP, such as magnetization and photosensitizing, provide additional capabilities and functions for improving delivery of the radioisotopes and monitoring the response to radiotherapy.

Examples of radiolabeled NP for therapeutic medicine include multi-layered gold coated ^{225}Ac NP for targeted alpha-particle

radiotherapy (Figure A.5) (McLaughlin *et al*., 2013) and NP containing ^{198}Au for potential prostate cancer treatments (Figure A.6) (Chanda *et al*., 2010). Since it is very difficult to deliver drugs across the blood-brain barrier, it was hypothesized that NP may act as vehicles to cross this otherwise rather tight body membrane. Particularly in brain tumor treatment, efforts are underway to functionalize the surface of NP with target molecules to brain endothelium and load them with the anti-cancer drug doxorubicin. In order to follow the fate of these conjugates, the polymer NP were radiolabeled with ^{14}C (Ambruosi *et al*., 2005; 2006). Indeed, the authors were able to show that only functionalized NP conjugates were able to cross the blood-brain barrier and they also demonstrated that the anti-cancer drug caused tumor reduction in a glioblastoma-bearing rat model. Yet, there is tremendous development of novel NP for therapeutic nanomedicine applications. The NP are engineered such that they are able to carry various functional groups like the drug molecule for treatment, target molecules for enhanced deposition in the tumor tissue and labeling molecules including, eventually, radiolabeled molecules. Several reviews summarize these efforts (Davis *et al*., 2008; Etheridge *et al*., 2013; Harisinghani *et al*., 2003; Harries *et al*., 2005; Lobatto *et al*., 2011). Also during hyperthermic treatment of brain tumors, magnetic NP were radiolabeled with the positron emission tomography tracer ^{18}F for visualization of appropriate targeting of the functionalized NP constructs (Plotkin *et al*., 2006).

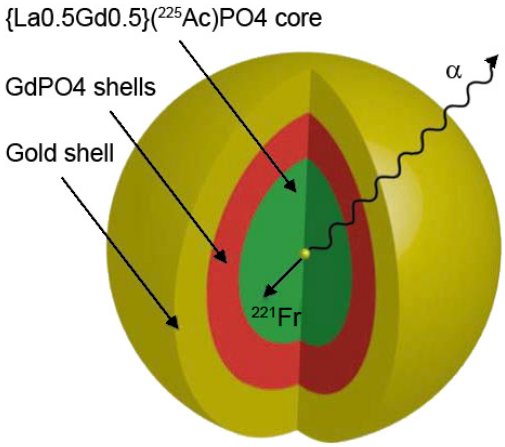
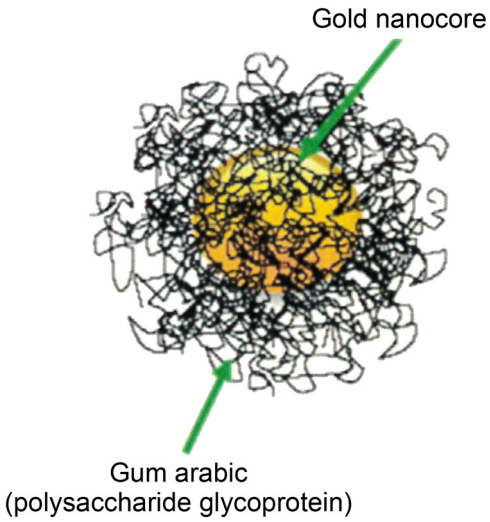


Fig. A.5. Schematic of gold coated lanthanide phosphate NP (McLaughlin *et al*., 2013).



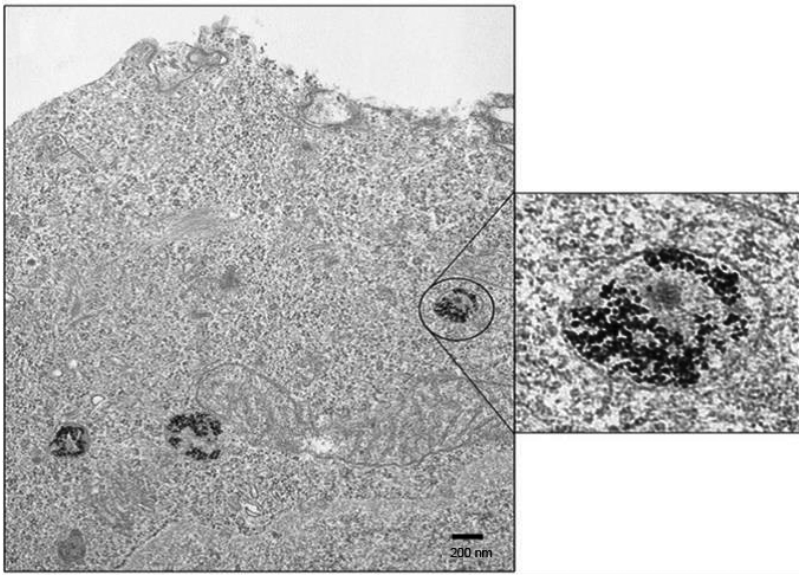


Fig. A.6. (Top) Schematic representation of gum Arabic glycoprotein functionalized ^{198}AuNP (GA-^{198}AuNP); (bottom) transmission electron microscope image showing uptake of GA-^{198}AuNP in prostate cancer cells (Chanda *et al.*, 2010).

A.6 Use of Radiation-Induced Emissions and Hyperthermal Effects from Nanoparticles in Therapeutic Medicine

In brachytherapy, the administration and preferential accumulation of GNP in tumor vasculature has been investigated as an opportunity to enhance the radiation dose to tumor vascular endothelial cells (Ngwa *et al*., 2012; Sinha *et al*., 2015). Administering GNP during brachytherapy for tumors such as prostate tumors would lead to dose enhancement through the radiation-induced photo/Auger electrons originating from the GNPs when irradiated by brachytherapy sources such as ^{131}Cs, ^{125}I, ^{103}Pd, ^{169}Yb, and 50 kVp x rays.

Martinez-Rovira and Prezado (2015) investigated the extent to which the outcome of radiotherapy can be improved by combining irradiation with dose enhancers such as high atomic-number (Z) NP in procedures such as proton therapy. Through Monte-Carlo calculations they showed a negligible increase of local energy deposition when the source was located at the NP surface. They noted that this dose enhancement was reduced when the source was located at further distances (*i.e*., in more realistic situations), and that, additionally, no significant increase in the dissociative electron attachment processes was observed. They hypothesize that physical effects may play a minor role in the amplification of damage to tumor cells, as a very low dose enhancement or increase of dissociative electron attachment processes was observed when their modeling used conditions closer to more realistic simulations. Thus, other effects, such as biological or chemical processes, may be mainly responsible for the enhanced radiosensitivity observed in biological studies. They recommend that more biological studies be conducted to verify this hypothesis.

Berbeco *et al*. (2016) examined the potential increase in tumor blood vessel endothelial cell radiation dose enhancement through the use of a linear accelerator target that can toggle between low-Z and high-Z targets during beam delivery. They note that use of the fast-switching target can enable modulation of the photon beam during delivery, producing a customized photon energy spectrum for each specific situation.

Paudel *et al*. (2016) demonstrated that GNPs generate OH radicals in aqueous media when they are exposed to a microwave field. Thus, combining the administration of GNPs with microwave irradiation has promise for the treatment of tumors. They note that it may be possible to generate OH radicals close to deoxyribonucleic acid of cells by proper localization of the NPs, and that NP-aided microwave hyperthermia may yield cell killing *via* both elevated temperature and free radical generation.

Appendix B

Biokinetic Models

B.1 Fate of Nanoparticles in the Lungs

Knowledge of the biokinetics of inhaled biopersistent nanometer- and micrometer-sized particles (NP and micrometer-sized particles) is essential as the basis for dosimetric and toxicological evaluations, which are necessary for performing risk assessments. Particles do not remain at their sites of deposition in the respiratory tract, but undergo numerous transport processes within the various tissues of the lungs, including clearance out of the lungs. Translocation rates are very low, dependent on portal of entry, particle size and surface characteristics (Figure B.1). In this context a

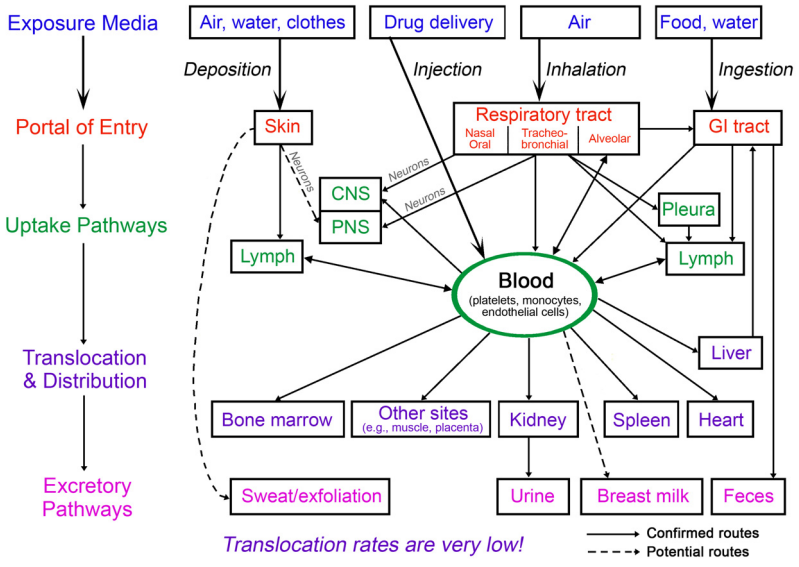


Fig. B.1. Exposure and biokinetics of NPs (adapted from Oberdorster *et al.*, 2005).

crucial question is how the results of biokinetic studies performed in animals can be extrapolated to humans. Importantly, particle clearance from the alveolar region of the lungs for rodents (except guinea pigs) is much more rapid than for humans, simians and canines.

The predominant long-term clearance pathway for both NP and micrometer-sized particles is macrophage-mediated particle transport from the peripheral lungs toward the ciliated airways and larynx. This is true for human and all other mammalian species, with the transport rates in rodents being 10 times higher than that in humans, nonhuman primates, and dogs.

Besides particle clearance out of the lower respiratory tract, there also is particle redistribution of deposited particles within the thoracic structures (interstitium, lymph nodes, and pleura) and particle translocation to the blood and lymph circulation with subsequent accumulation in secondary organs. Lymphatic clearance of inhaled particles deposited in the lung involves two pathways for particles reaching the pulmonary interstitium: one is directly to the hilar (tracheobronchial) lymph nodes, while the other is *via* translocation to the pleural spaces with subsequent uptake by lymphatic stomata in the parietal pleura and transport to mediastinal lymph nodes (Donaldson *et al*., 2010). While these clearance mechanisms operate for all persistent particles, it is especially important for fibrous particulates because fibers reaching the pleural space are not cleared if they are too long for uptake by the stomata. Such fibers (*e.g*., asbestos) can initiate pleural pathology such as granuloma and mesothelioma induction. Evidence for the pleural clearance pathway in humans is found in coal miners, with findings of black spots in the parietal pleura (Figure B.2).

While micrometer-sized particles at low lung burdens enter interstitial spaces in the rodent lungs to a limited degree only, NP can be rapidly taken up by and translocated across the epithelium to enter the underlying interstitium. Additional evidence in rat studies shows that they do not form an interstitial sequestration compartment but rather they re-enter the airways (Semmler-Behnke *et al*., 2007). However, the location for re-entry (possibly alveolar structures or bronchus-associated lymphoid tissue in the conducting airways) has not been definitely defined (Ferin and Oberdorster, 1992b; Ferin *et al*., 1992). In contrast, there also is indirect evidence that both NP and micrometer-sized particles are translocated into the epithelium and interstitial spaces of the human, simian and canine lungs to form a persistent interstitial sequestration compartment (Gregoratto *et al*., 2010; Kreyling *et al*., 2014; Nikula *et al*., 1997).

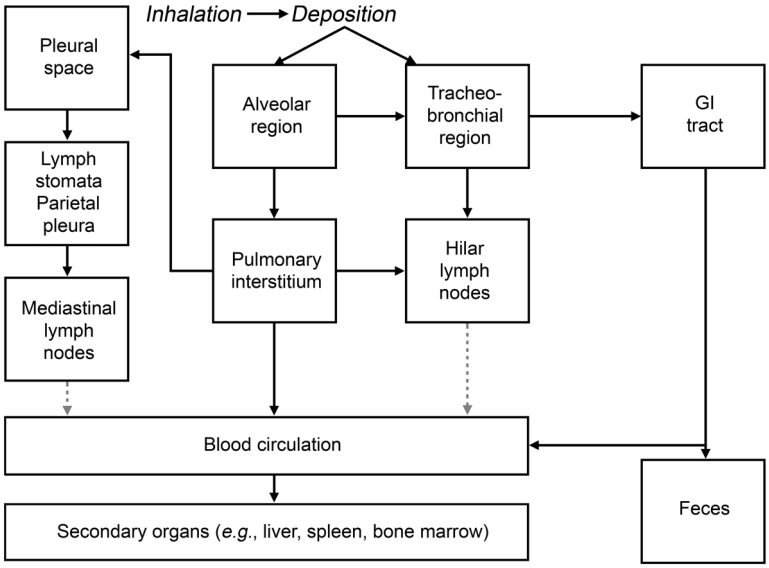


Fig. B.2. Lymph clearance of fibrous and nonfibrous particles from the lungs. Translocation pathways of deposited particles in the lung that reach the interstitium are *via* lymphatic channels to hilar lymph nodes, or migration toward the pleura with subsequent uptake into lymphatic openings (stomata) and clearance toward mediastinal lymph nodes. Both hilar and mediastinal lymph nodes drain into the right lymphatic duct to reach the jugular vein in the neck area (indicated by dashed gray arrows). Dissolution of soluble or partially soluble particles will occur along the translocation route, depending on dissolution rate in surrounding milieu (*i.e.*, such parameters as pH) (adapted from Oberdorster *et al.*, 2013).

A separate pathway of clearance of NP from the respiratory tract involves the movement of NP that have deposited in the olfactory mucosae along olfactory neurons to the olfactory bulb in the brain. This translocation pathway has been well established in experimental animal models using both nasal instillation and inhalation routes of exposure in rodents and nonhuman primates. Moreover, NP translocation *via* sensory trigeminal neurons of the nasal cavity to the trigeminal ganglion at the base of the brain has been described (Hunter and Dey, 1998). This neuronal translocation may be significant as it circumvents the tight blood-brain barrier (Oberdorster *et al.*, 2009). Additionally, the penetration efficiencies may not be trivial, ranging from <1 to >10 % of the deposited NP (*e.g.*, Elder *et al.*, 2006), depending on NP surface chemistry, dose, particle size, and exposure method (Oberdorster *et al.*, 2009).

Only limited data about long-term retention of repeatedly inhaled NP are available, including subchronic inhalation studies with ultrafine TiO_2 (Bermudez *et al*., 2004) and ultrafine carbon black (Elder *et al*., 2005) in rats and mice, showing lung burden dependent prolongation of the clearance of the lung burden in the post-exposure period. In a more recent study, Creutzenberg (2013) determined pulmonary retention half-time of three different TiO_2 NP following a 28 d nose-only inhalation exposure in rats at three concentrations (3, 12, and 48 mg m^{-3}) of each material with a 90 d post-exposure period. Lung burden at 0, 45, and 90 d post-exposure, but no fecal excretion, were measured. For all three TiO_2 NP, pulmonary clearance at the lowest concentration occurred with physiological rat-specific retention half-life ($T_{1/2}$) between ~50 to 80 d; in contrast, the mid- and high-concentration exposed rats showed significant retarded clearance with half-life ranging between 160 to 270 d (mid-concentration) and 315 to 480 d (high concentration). This indicates that lung clearance kinetics of poorly soluble NP are not different from those of larger-sized micrometer-sized particles showing the well-known phenomena of particle lung overload retarded clearance described by Morrow (1988). However, in contrast to Morrow's hypothesis of volumetric loading impairing alveolar macrophage function, the underlying mechanism may be different as indicated by results of a 12-week inhalation study with nano-TiO_2. In this study, a nano-TiO_2 volume load of alveolar macrophages far below volume overload resulted in an eight-fold prolongation of the particle retention $T_{1/2}$ (Oberdorster *et al*., 1994).

Because nano-TiO_2 can be regarded as a more benign NP, it should not be viewed as representative for ENP in general. NIOSH (2011) has provided a REL for occupational exposure to nano-TiO_2 of 0.3 mg m^{-3}, and for micro-TiO_2 of 2.4 mg m^{-3} as a result of different specific surface areas. In contrast, based on results of subchronic rat inhalation studies with MWCNT, NIOSH (2013b) derived a REL of only 1 μg m^{-3} for CNT and CNF.

B.2 Particle Clearance and Translocation Pathways

Figure B.3 illustrates a clearance model for poorly soluble particles in the gas exchange region of the human respiratory tract (Gregoratto *et al*., 2010). In the model, a persistent interstitial sequestration compartment consisting of ~40 % of the alveolar deposited dose was based on data from six cohorts of radio-aerosol exposed workers.

Translocation into circulation followed by accumulation in secondary organs and tissues of the body is limited only to NP with the

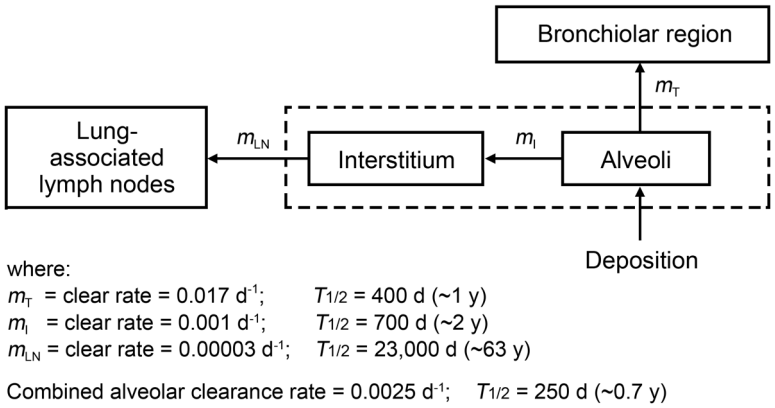


Fig. B.3. Clearance model for poorly soluble particles in the gas exchange region of the human respiratory tract [Gregoratto *et al*., 2010 (based on the Kuempel *et al*., 2001 model)].

exception of severe particle overload conditions for micrometer-sized particles. It also has been shown that large lung contents of alpha-emitting micrometer-sized particles of $^{239}PuO_2$ can result in the translocation of intact particles to blood (Guilmette *et al*., 1987). However, it is not clear whether the movement of the micrometer-sized particles occurred *via* the lung capillaries or the lung-associated lymph nodes. Translocated NP fractions are rather small but they depend strongly on the physicochemical properties of the NP, specifically their surface properties. There is growing evidence from *in vitro* studies that binding (including coating) and conjugation of proteins to NP may play an essential role in translocation across cellular membranes and organ barriers. Thus, along this translocation process, it is thought that NP surfaces will undergo dynamic changes through a process defined as "corona formation" by proteins and lipids (Walczyk *et al*., 2010). However, detailed information on this process *in vivo* is still lacking.

The dimensions of NP are also similar in size to the dimensions of many cellular materials and processes and might therefore be disruptive. For example, NIOSH (2013b) reported that results from *in vitro* studies with human lung cells have shown the ability of SWCNT to cause genotoxicity and abnormal chromosome number, because of interference with mitosis (cell division), by disrupting the mitotic spindles in dividing cells and inducing the formation of anaphase bridges among the nuclei (Kisin *et al*., 2011; Muller *et al*., 2008; Sargent *et al*., 2009; 2012). NIOSH (2013b) notes, however, that other *in vitro* studies of some MWCNT did not show evidence

of genotoxicity (Kim *et al*., 2011; Wirnitzer *et al*., 2009), indicating the importance of NP-specific properties.

In summary, particle biokinetics involve a multitude of highly dynamic processes that depend not only on physicochemical properties of the particles but also on a variety of cellular and molecular mechanisms and interactions. Main clearance pathways include uptake by epithelial cells, interstitial translocation into lymph and blood circulation, and uptake of some NP by macrophages with clearance toward the mucociliary escalator. Data indicate that interstitialized NP can re-enter airspaces, which could either be in the alveolar or BB/bb (Ferin and Oberdorster, 1992b; Ferin *et al*., 1992) where they are found phagocytized by macrophages (Figure B.4) (Semmler-Behnke *et al*., 2007). Only 20 % or less of the contemporary lung burden can be lavaged from the airways at any long-term retention time point, while the remaining ~80 % is still retained in the lungs (intra-epithelial and interstitial spaces) and is gradually cleared *via* the airways and larynx. Thus, these particles need to re-entrain onto the lung surface for macrophage-mediated clearance to take place.

Given the rather low translocation to and accumulation in secondary organs after acute NP inhalation exposures, it appears likely that adverse effects caused by NP accumulated in secondary organs would mainly occur during chronic exposures over an extended period of time. Hence, adverse health effects in secondary organs like the cardiovascular system associated with chronic exposure of ambient urban air pollution, including ultrafine particles, can involve several pathophysiological mechanisms [*e.g*., triggering systemic acute phase responses *via* mediators released in the lungs, or activating sensory neurons in the conducting airways affecting the autonomous nervous system (Pope and Dockery, 2006)].

B.3 Exposure and Biokinetics of Ingested Nanoparticles

Today many nanostructured materials such as TiO_2 NP or SiO_2 NP are used in food additives. Furthermore, engineered nanomaterials containing drugs can be administered *via* several pathways: intravenous injection, inhalation as well as ingestion. For these medical applications, the oral route is the most convenient route since it is noninvasive and widely accepted by most of the patients. Particles deposited *via* inhalation in the posterior nasal passages and in the lower respiratory tract can also be transported as particles by mucociliary clearance to the larynx and swallowed into the GI tract. It is generally believed that absorption across the intestinal membrane to the circulation is somehow dependent on size (Florence, 2005; Powell *et al*., 2010; Ruenraroengsak *et al*., 2010).

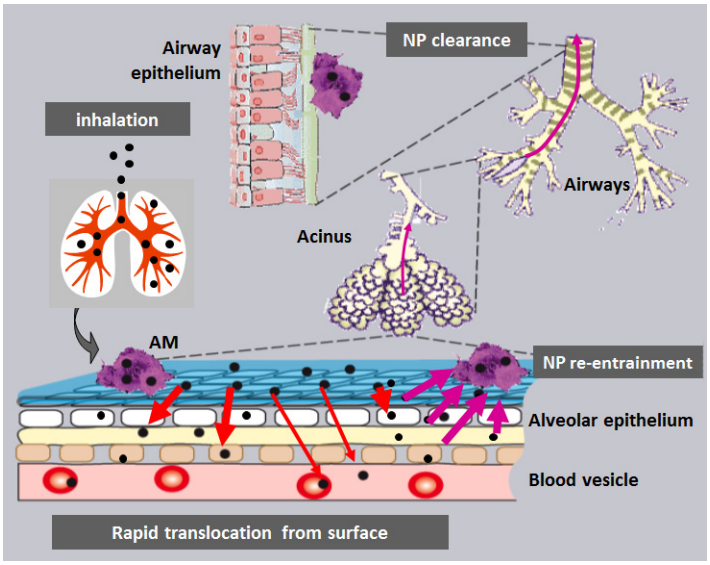


Fig. B.4. Kinetics of inhaled 20 nm sized single, poorly soluble NP (iridium, gold, TiO_2) in the lung of rats following deposition in the alveolar region (adapted from Kreyling *et al*., 2013; Semmler-Behnke *et al*., 2007).

However, little is known about the uptake of NP across the GI membranes and the following accumulation in secondary target organs.

Jones *et al*. (2015) administered 10 nm, 70 nm, or 1.8 μm diameter pigment grade TiO_2 as a single 5 mg kg^{-1} body weight oral dose to human volunteers and found systemic absorption of the NP across the gut epithelium to be <0.1 %. Konduru *et al*. (2015) studied how the presence or absence of an amorphous silica coating on the surface of ^{141}Ce-radiolabeled CeO_2 NP influences the pharmacokinetics and pulmonary effects of the NP following intratracheal instillation, gavage, and intravenous injection in rats. Post-gavage, nearly 100 % of both NPs were excreted in the feces, consistent with very low gut absorption.

Ojer *et al*. (2012) conducted biodistribution and acute and subacute toxicity studies of ^{99m}Tc-labeled poly(anhydride) NP to assess their potential use as carriers for oral drug/antigen delivery. The biodistribution studies demonstrated that these carriers remained in the gut with no evidences of particle translocation or distribution to other organs.

Schleh *et al*. (2012) quantitatively investigated the biodistribution in rats after oral gavage of ^{198}Au radiolabeled, monodisperse, negatively charged gold spheres of core diameters of 1.4, 5, 18, 80,

and 200 nm, as well as negatively and positively charged 2.8 nm GNP. The highest absorption across intestinal barriers was found for 1.4 nm GNP, whereas for the 2.8 nm NP, the negative charge was favored over positive charge. However, size and surface charge were not responsible alone, since 18 nm NP were absorbed more than the 5 nm particles and the 18 nm NP had the highest accumulation in the brain. Schleh *et al*. attributed the variations in NP accumulation to the possibility of "selected protein binding." Overall, Schleh *et al*. found the total absorption of NP to the circulation to be <1 % during the 24 h period following gavage, with fecal excretion accounting for >99 % of the delivered GNP.

Evaluations of the possible absorption of intact NP from the gut are more challenging when the NP are more soluble. In a study by Hughes *et al*. (2012) of the whole-body retention and distribution of orally administered ^{59}Fe-radiolabeled zerovalent iron NP in mice, NP that had been subjected to neutron-activation were administered by oral gavage. After three repeated daily doses, Hughes *et al*. found that 35 % of the radioactivity delivered through the oral route was eliminated through the feces, 35% was in the liver, and 23% was in blood. They noted that the translocation of radioactivity from the GI tract may have been associated with dissolved material, rather than with any translocation of intact NP.

In a study by Pele *et al*. (2015), human volunteers with normal intestinal permeability were orally administered 100 mg pharmaceutical/food grade anatase titanium dioxide, and blood samples were collected from 0.5 to 10 h post ingestion and analyzed by dark field microscopy for the presence of "reflectant bodies" (particles) in the blood, and by inductively coupled plasma mass spectrometry for the presence of total titanium in the blood. Pele *et al*. reported that their observation of reflectant particles by microscopy in blood roughly mirrored the levels of total titanium observed by the inductively coupled plasma mass spectrometry, providing some qualitative evidence that whole particles had been absorbed. They recommended that additional quantitative experiments be conducted to better determine the fractional uptake of intact NP from the gut.

As indicated by results of the studies of Jones *et al*. (2015), Kondura *et al*. (2015), Ojer *et al*. (2012), and Schleh *et al*. (2012), absorption of intact NP from the GI tract does not appear to occur at more than fraction-of-a-percent amounts; nearly all of the ingested amounts of poorly soluble NP in those studies were found to be excreted in the feces. Future studies could be directed at clarifying mechanisms of GI tract absorption and translocation involving bioprocessing of NPs in the epithelium.

B.4 Human and Animal Studies Using Radioactive Nanoparticles

Table B.1 provides a review of human and animal studies by species, administration, study, size, RNP, radionuclide, radionuclide generation, and specific reference.

TABLE B.1—*Selected animal studies using RNPs.*

Species[a]	Administration[b]	Study[c]	RNP[d]	Size[e] (nm)	Radionuclide	Radionuclide Source[f]	Reference
Agricultural crops	UR	TL, UP, BD, IM	MWCNT	—	^{14}C	—	Larue *et al.* (2012)
Hamster	II	BD	Albumin nanocolloids	80	^{99m}Tc	Reactor fission products	Nemmar *et al.* (2001)
Human	IH	DP, TL (none)	EC NP (technegas)	100	^{99m}Tc	Reactor fission products	Mills *et al.* (2006)
Human	IH	DP, CL	EC NP (technegas)	40 + 100	^{99m}Tc	Reactor fission products	Moller *et al.* (2004; 2006)
Human	IH	DP, CL	EC NP (technegas)	35 + 100	^{99m}Tc	Reactor fission products	Wiebert *et al.* (2006a; 2006b)
Human and mouse	CC	UU	Magnetite Fe_3O_4 NP	100	^{56}Co	Proton beam on Fe_3O_4 NP	Marmorato *et al.* (2011)
Mouse	IH	BD	TiO_2 NP	—	^{48}V	—	Geiser *et al.* (2014)
Mouse	IH	BD	Iridium NP	—	^{192}Ir	—	Geiser *et al.* (2014)
Mouse	IV	BD	GNP conjugated with albumin or other	15 + 80	^{198}Au	Reactor neutron activation	Schaffler *et al.* (2014)

Mouse	IV	BD	GNP conjugated with albumin or other	15 + 80	^{198}Au	Reactor neutron activation	Schaffler *et al.* (2014)
Mouse	IV	IM, PK, BD	SPIO NP-labeled macrophages	—	^{111}In	—	Wu *et al.* (2014)
Mouse	IV	BD, TU	Perfluoro-pentane gas filled Fe-SiO_2 nanoshells	500	^{111}In	—	Liberman *et al.* (2013)
Mouse	IV	BD, PK	Lipidots (coated)	55	^{3}H-hydrocarbons	—	Merian *et al.* (2013)
Mouse	IH	BD	GNP	20	^{195}Au	Proton beam cyclotron	Schleh *et al.* (2013)
Mouse	IV	BD, TT	Protein-based NP	33 to 36	^{99m}Tc	Reactor fission products	Yang *et al.* (2013)
Mouse	IV	IM, MT	Annexin A5-conjugated core-cross-linked polymeric micelles (CCPMs)	—	^{111}In	—	Zhang *et al.* (2013)
Mouse	IV	BD, TX	PEGylated poly(n-butylcyano-acrylate) (PBCA) NP	—	^{99m}Tc	Reactor fission products	Chaudhari *et al.* (2012)

TABLE B.1—(*continued*)

Species[a]	Administration[b]	Study[c]	RNP[d]	Size[e] (nm)	Radionuclide	Radionuclide Source[f]	Reference
Mouse	CI	BD, VC	Brucella ovis (HS) in mannosylated NP (MAN-NP-HS)	300	^{99m}Tc	Reactor fission products	Da Costa Martins *et al.* (2012)
Mouse	—	BD, TT	Nano-graphene oxide sheets (conjugated)	—	^{66}Ga	—	Hong *et al.* (2012)
Mouse	OG	BD, UP	Zerovalent Fe NP	—	^{59}Fe	Reactor neutron activation	Hughes *et al.* (2012)
Mouse	OG	BD, IM	ZnO	20 or 100	^{18}F	—	Lee *et al.* (2012)
Mouse	IV	PC, BD, IM	$CoFe_2O_4$ (stabilized, 3 materials)	—	^{99m}Tc	Reactor fission products	Psimadas *et al.* (2012)
Mouse	IV	BD	Cd/Se Quantum Dots (coated)	14 + 17	^{109}Cd	—	Sun *et al.* (2012)
Mouse	IV	BD, TU	DOTA phage NP	—	^{64}Cu	—	Li *et al.* (2011a)
Mouse	IV	BD	AMC NP (coated)	—	^{188}Re	—	Tang *et al.* (2011)
Mouse	IV	BD, CL	Etoposide-loaded poly(lactic-co-glycolic acid) NP	105 + 160	^{99m}Tc	Reactor fission products	Yadav *et al.* (2011)

Mouse	IV	BD	Oxidized MWCNT or graphene oxide nanoplatelets	—	^{99m}Tc	Reactor fission products	Li *et al.* (2011b)
Mouse	IV	II	Ag NP (capped with PVP)	12	^{125}I	—	Chrastina and Schnitzer (2010)
Mouse	IV	IM, BD	Na^{125}I in SWCNT	—	^{125}I	—	Hong *et al.* (2010)
Mouse	IV	IM, BD, CL, TX	ORMOSIL NP	20 to 25	^{124}I	—	Kumar *et al.* (2010)
Mouse	IV	BD	siRNA with Chitosan, liposomes or JetPEI	—	^{32}P	—	Gao *et al.* (2009)
Mouse	—	BD	DOTA-GlyGlu-Cyc MSH	—	^{111}In	—	Guo *et al.* (2009)
Mouse	IV	BD	siRNA in PEI_ PEG – PEI poly-plexes	>200	^{99m}Tc	Reactor fission products	Merkel *et al.* (2009a; 2009b)
Mouse	IV	IM, PK	Magneto-fluorescent NP (coated)	20	^{64}Cu	—	Nahrendorf *et al.* (2008)
Mouse	IV	BD	Quantum dots	3 to 8	^{99m}Tc	Reactor fission products	Choi *et al.* (2007)
Mouse	IV	BD, TT	Thiolated gelatin NP (with PEG)	150 to 250	^{111}In	—	Kommareddy and Amiji (2007)

TABLE B.1—(*continued*)

Species[a]	Administration[b]	Study[c]	RNP[d]	Size[e] (nm)	Radionuclide	Radionuclide Source[f]	Reference
Mouse	IV	CL	SWCNT (coated)	—	^{111}In	—	Singh *et al.* (2006)
Mouse	IV	BD, TU	PEO-modified PBA ester	—	^{111}In	—	Shenoy *et al.* (2005)
Mouse	IV	BD, TU	^{3}H-paclitaxel in Polymeric NP	—	^{3}H	—	Shenoy *et al.* (2005)
Mouse	IV	II	PEGylated nano-graphene oxide	—	^{89}Zr, ^{64}Cu, ^{66}Ga	—	Chopra (2004a; 2004b; 2004c)
Mouse and rat	IV	IM	Au + PAMAM dendrimers	5 to 25	^{198}Au	Reactor neutron activation	Bielinska *et al.* (2002)
Mouse and rat	IV	BD, EL	Poly(methyl-2- ^{14}C-methacrylate NP	—	^{14}C	—	Kreuter *et al.* (1979)
Rat	II	BD, TL, AC	GNP stabilized by triphenyl-phosphene	1.4, 2.8, 5, 18, 80, 200	^{198}Au	Reactor neutron activation	Kreyling *et al.* (2014)
Rat	IV	TT	GNP core with DTPA shell	—	^{99m}Tc, ^{111}In	Reactor fission products	Alric *et al.* (2013)
Rat	II	BD	SWCNT	—	^{125}I	—	Lin *et al.* (2014)

Rat	OG	TX, BD	Poly(anhydride) NP, NP-HPCD, NP (coated 6000)	180	^{99m}Tc	Reactor fission products	Ojer *et al.* (2012)
Rat	OG	BD, TL, AC	GNP (coated)	1.4, 2.8, 5, 18, 80, 200	^{198}Au	Reactor neutron activation	Schleh *et al.* (2012)
Rat	IH	BD	Iridium	20	^{192}Ir	Reactor neutron activation	Semmler-Behnke *et al.* (2012)
Rat	IV	BD, TL, AC	GNP (coated)	1.4, 2.8, 5, 18, 80, 200	^{198}Au	Reactor neutron activation	Hirn *et al.* (2011)
Rat	IH	BD	TiO_2 anatase	10 to 50	^{48}V	Proton beam cyclotron	Kreyling *et al.* (2011)
Rat	IT, IV, OG	BD	CeO_2	33	^{141}Ce	—	Konduru *et al.* (2015)
Rat	IV	BD, IM	Hybrid Ga_{203} NP (poly-siloxane shell)	3 to 4	^{111}In	—	Kryza *et al.* (2011)
Rat	IV	BD, EL, PK	PAA NP (coated/non coated)	31	^{14}C	—	Wenger *et al.* (2011)
Rat	IV and IT	BD	GNP (coated)	5	^{198}Au	Reactor neutron activation	Lipka *et al.* (2010)
Rat	IV	BD, IM	Poly(lactic-co-glycolic acid)	130	^{99m}Tc	Reactor fission products	Subramanian *et al.* (2010)

TABLE B.1—(*continued*)

Species[a]	Administration[b]	Study[c]	RNP[d]	Size[e] (nm)	Radionuclide	Radionuclide Source[f]	Reference
Rat	IV	BD	MWCNT	—	^{14}C	—	Georgin *et al.* (2009)
Rat	IH	BD, TL, AC	Iridium + EC	20 + 80	^{192}Ir	—	Kreyling *et al.* (2009)
Rat	IV	BD	Fullerene C_{60} nanocrystals	200 to 250	^{125}I	—	Nikolic *et al.* (2009)
Rat	IT, IV	BD, TL, AC	GNP (coated)	1.4 + 1.8	^{198}Au	Reactor neutron activation	Semmler-Behnke *et al.* (2008)
Rat	IT, IV	BD, TL, AC	GNP (coated)	1.4 + 1.8	^{198}Au	Reactor neutron activation	Semmler-Behnke *et al.* (2007)
Rat	IH	BD, TL, AC	Iridium	20	^{192}Ir	Reactor neutron activation	Semmler *et al.* (2004), Semmler-Behnke *et al.* (2007)
Rat	IV	BD, TT	Poly(n-butyl cyanoacrylate) NP (coated)	~200	^{14}C	—	Ambruosi *et al.* (2005; 2006)
Rat	IU (lung perfusion)	TL	Iridium	18	^{192}Ir	Reactor neutron activation	Meiring *et al.* (2005)

Rat	Brain perfusion	BD	E78 NP and E72 NP	—	^{3}H	—	Koziara *et al.* (2003)
Rat	IH	BD, TL, AC	Iridium	20	^{192}Ir	Reactor neutron activation	Kreyling *et al.* (2002a; 2002b)
Rat	II	TP	Latex NP	20 to 1,000	^{125}I	—	Brooking *et al.* (2001)
Rat	IV	BD	Poly(methyl methacrylate) NP (coated)	130	^{14}C	—	Araujo *et al.* (1999a; 1999b)
Rat	IV	BD	Amorphous SiO_2 (coated)	200 to 500	^{75}Se	—	Borchard and Kreuter (1996)
Rat	IV	—	PAMAM NP (coated)	—	^{75}Se	—	Borchard *et al.* (1994)
Rat	IV	BD, IM	SPIO NP (coated)	—	^{111}In	—	Schaffer *et al.* (1993)
Rat	IV	BD	PMM NP (coated)	—	^{14}C	—	Troster and Kreuter (1992)

[a]Species include human and animal models developed for specific work including: mouse model of cystic fibrosis, normal and metastatic melanoma-bearing C57 mice, 4T1 tumor-bearing mice, breast tumor (MDA-MB-435)-bearing and nontumored nude mice, and others.

[b]Administration methods include:

BP	=	*in situ* brain perfusion	IU	= instillation unspecified
CC	=	cell culture incubation	IV	= intravenous injection
CI	=	conjunctival instillation	OG	= oral gavage
IH	=	inhalation	UR	= uptake by plant roots
II	=	intranasal instillation	UU	= uptake unspecified
IT	=	intratracheal instillation		

[c]Studies (*i.e.*, the aim or purpose of the animal study) include:

AC	=	accumulation	PC	= determining physicochemical properties
BD	=	biodistribution	TT	= tumor targeting or treatment
BE	=	bioeffects	TU	= tumor uptake
CL	=	clearance	TX	= toxicity
DP	=	deposition	UP	= uptake
EL	=	elimination	VC	= vaccination
GC	=	generation and characterization	PK	= pharmacokinetics
IM	=	imaging	RT	= retention
MT	=	molecular tomography	TL	= translocation
OP	=	organ perfusion	TP	= transportation

[d]AMC = aluminum matrix composite
C_{60} = spherical carbon molecule with the formula C_{60}
DOTA = tetraazacyclododecane-1,4,7,10-tetraacetic acid
GNP = gold nanoparticle
RNP = radioactive nanoparticle
E72 NP = polyoxyl 2 stearyl ether (Brij 72) nanoparticles
E78 NP = emulsifying wax nanoparticles
EC = elemental carbon
MWCNT = multi-walled carbon nanotube
NP = nanoparticle
ORMOSIL = organically modified silica
PAA = polyacrylic acid
PAMAM = polyamidoamine
PEG = polyethylene glycol
PEO = polyethylene oxide
PVP = polyvinylpyrrolidone
RNP may be identified as "coated" which could be by: ionic molecules Such as citrate, polysorbate 80, poloxamine 908, plasma proteins, and other materials.
SPIO = super-paramagnetic iron oxide

[e]Sizes are given for primary particles which usually buildup larger agglomerates/aggregates over time.

[f]Radionuclide sources include production by proton cyclotrons and other accelerators that involve beam interactions with target materials (*i.e.*, nuclear reactions) or by reactors involving neutron activation. Reactor production generally involves either neutron activation or fission products (reactor fission products; *e.g.*, $^{99}Mo \rightarrow {}^{99m}Tc$) while proton cyclotrons and other accelerators often involve other nuclear reactions.[c]

Appendix C

Key Concepts for Understanding Nanoparticle Aerosol Properties and Behaviors

C.1 Introduction

The reference text book *Radioactive Air-Sampling Methods* (Maiello and Hoover, 2010a) summarizes important properties and behaviors of airborne radioactive particles of all sizes. An associated online resource addresses a number of radioactive air-sampling problems and solutions (Maiello and Hoover, 2010b). Cash (2014) adapted and applied that information to understanding and managing the characteristics and behavior of RNP, with an emphasis on plutonium oxides. The aerosol technology text books by Hinds (1999) and Kulkarni *et al*. (2011a) provide extensive information about the properties, behavior and measurement of airborne particles in general. Based on those references, and as delineated in the following sections, key concepts for understanding the properties and behaviors of NP in general and RNP in particular are that:

- a range of mechanisms influence particle motion and collection;
- behavior of airborne NP is dominated by Brownian diffusion, while larger particle behavior is dominated by inertia;
- particle volume equivalent diameter, thermodynamic diameter, and aerodynamic equivalent diameter are related;
- particle size distributions are frequently lognormal;

- NPs dominate the count distribution, while larger particles dominate the mass distribution;
- NPs exist to some extent in the majority of occupational aerosols;
- smaller particles have a greater fraction of their atoms at the particle surface;
- number concentrations of concern depend on the material of concern;
- realistic airborne PNCs can be limited by coagulation; and
- smaller particles are more difficult to dislodge from surfaces than larger particles.

These concepts are considered below with some practical illustrative examples.

C.2 A Range of Mechanisms Influence Particle Motion and Collection

As shown in Figure C.1, mechanisms influencing particle motion and collection on surfaces, including the respiratory tract, include: gravitational sedimentation, inertia, interception, Brownian diffusion (also known as thermal diffusion), and electrostatic attraction. Knowledge of the particle size distribution is needed to estimate the dominant mechanisms of motion that will govern particle behavior in general and deposition mechanism in particular.

C.3 Behavior of Airborne Nanoparticles is Dominated by Brownian Diffusion

While larger particle behavior is dominated by inertia, NP behavior is dominated by Brownian diffusion. As shown in Figure C.2, particle size dictates the relative influence on particle motion of gravitational sedimentation (*i.e.*, vertical displacement) and diffusion mechanisms (*i.e.*, the root mean square distance the particle travels as a result of Brownian motion). The figure example is for unit-density spheres. Note that logarithmic scales are required on both axes to address orders-of-magnitude differences in the degrees of displacement and particle diameters of interest. As shown on the left-hand side of the figure, displacement of a 1 nm diameter particle by diffusion over the course of a 1 s time period is ~1 mm, while displacement by gravitational sedimentation in the same period is essentially not seen. In contrast, as shown on the right-hand side of the figure, displacement of a 10 μm diameter particle by diffusion over the course of a 1 s time period is essentially not seen, while displacement by gravitational sedimentation in the same

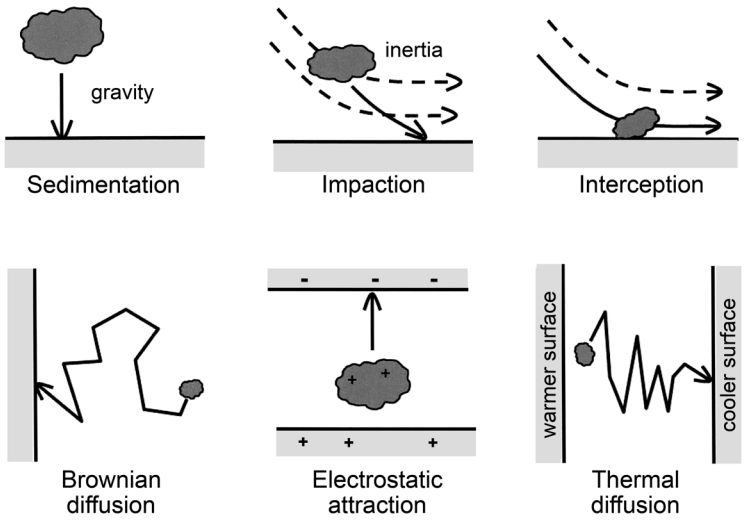


Fig. C.1. Fundamental mechanisms of particle collection in the environment, in air filtration and air cleaning systems, and in the human respiratory tract (Hoover, 2010b).

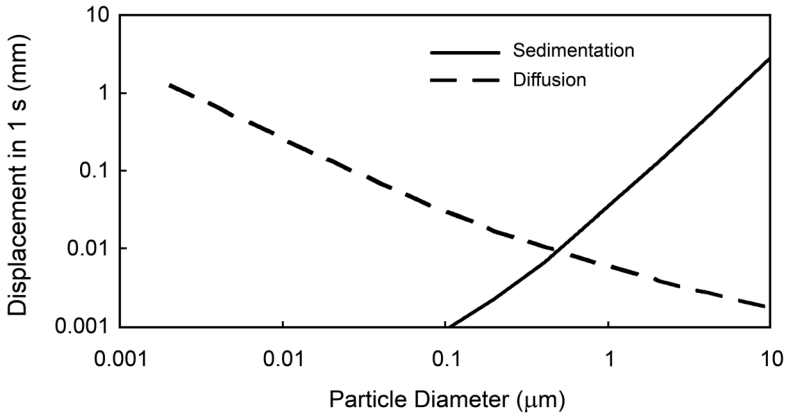


Fig. C.2. Comparison of the relative importance of gravitational sedimentation and Brownian diffusion on particle motion (Raabe, 1994).

period is several millimeters. In the transition region between diffusion-dominated (*i.e.*, thermodynamic) behavior and sedimentation-dominated (*i.e.*, aerodynamic) behavior, the influence of the two effects are essentially equal. Displacement is minimal for particles in the transition region. Because air velocities in ventilated work areas are often much greater than 10 mm s^{-1}, most particles in the size ranges at and below the transition region are transported by air flow (Wasiolek *et al.*, 1999; Whicker, 2010).

C.4 Particle Volume Equivalent Diameter, Thermodynamic Diameter, and Aerodynamic Equivalent Diameter are Related

The volume equivalent diameter (d_e), thermodynamic diameter (d_{th}), and aerodynamic equivalent diameter (d_{ae}) of a particle are all related, but the details of those relationships depend on the physical properties of the particles in question (*e.g.*, round smooth spheres, irregularly shaped but relatively compact particles, fibers, disks, or various forms of compact or branched-chain agglomerates) as well as on the manner in which various forces (*e.g.*, aerodynamic, diffusive, electrostatic) are applied to the particles during a situation of interest (*e.g.*, airborne behavior in the workplace, deposition in an aerosol sampling device, deposition in filter media, inhalation and deposition in the respiratory tract). Ideally, the results of a given aerosol measurement method would be relevant to a situation of interest such as aerosol behavior in the workplace or deposition in the respiratory tract. Unfortunately, the physical conditions during the measurement of aerosols in the workplace typically involve collection and handling conditions that are "not the same" as in the respiratory situation or other situations of interest. Differences can include internal instrument atmospheric pressures; possible applications of inertial, electrostatic, or other forces in the instrument in addition to gravity; possible drying or wetting of particles; or possible dilution or concentration of particle numbers per unit volume in the sampling device.

ICRP equates particle volume equivalent diameter d_e with particle thermodynamic diameter d_{th}, and provides formulas to calculate any of the diameters, based on knowledge of the others (assuming that information about particle shape and density are also known). Calculation of the aerodynamic equivalent diameter d_{ae} of a particle with thermodynamic diameter d_{th} (*i.e.*, volume equivalent diameter d_e) can be accomplished using the relationship presented in Section D.4.1 in Annex D of ICRP (1994a), which is shown in Equation C.1:

$$d_{ae} = d_{th}\sqrt{\frac{\rho C(d_{th})}{\chi \rho_o C(d_{ae})}}, \quad \text{(C.1)}$$

where:

ρ_o = default value of unit density (1 g cm^{-3})
ρ = actual density of the particle
χ = shape factor of the particle (which ranges from one for a sphere to two for a plate-like particle)
$C(d_{th})$ = Cunningham slip correction factor for a particle of thermodynamic diameter d_{th}
$C(d_{ae})$ = Cunningham slip correction factor for a particle of aerodynamic equivalent diameter d_{ae}

The value of the slip correction factor depends on the temperature, pressure and viscosity of the air. Note that as particle density increases, the value of d_{ae} increases by a factor that is approximately equal to the square root of the particle density. In other words, denser particles are aerodynamically larger.

As the value of the shape factor, χ, increases, the value of d_{ae} decreases. In other words, elongated or plate-like particles with a shape factor of two behave as if they are smaller than spherical particles of equivalent volume. Thus, particle shape has a secondary effect on particle behavior compared to the primary effect of particle size. The particle model used by ICRP uses a default value of 1.5 for the shape factor to relate physical diameter to aerodynamic or diffusion diameter. Investigations of how to appropriately assess the shape factor for complex particle shape, including agglomerates, across all particle sizes have been made over many years and are continuing (*e.g.*, DeCarlo *et al.*, 2004; Hinds, 1999; Kasper, 1982; Ku and Kulkarni, 2015; Kulkarni *et al.*, 2011b; Sorenson, 2011; Willeke, 1976).

Although it would be ideal if χ could be assigned based on directly measured geometric features of a particle or agglomerate, this area is still being investigated. The approach used by the investigators noted above basically involves making independent measurements of a diameter of interest (*e.g.*, the mobility equivalent diameter d_{mob} in a setting involving diffusion) and then solving for χ using the following equation which involves a number of simplifying assumptions:

$$\chi = \frac{d_{mob} C(d_{ve})}{d_{ve} C(d_{mob})}, \quad \text{(C.2)}$$

where:

d_{ve} = (the volume equivalent diameter) is the diameter of a sphere having the same volume as that of the irregular particle,
$C(d_{ve})$ = slip correction factor for d_{ve}
$C(d_{mob})$ = slip correction factor for d_{mob}

The volume equivalent diameter d_{ve} is obtained from the mass of the particle and the particle material density (ρ_p), which must be determined for the material of interest.

Confounding issues in the definitive measurement of "particle size" include how the force that is applied to a particle in a given situation (*e.g.*, gravity and natural diffusion only, acceleration through a nozzle, electrical mobility across a charged region) can potentially alter the shape, orientation, or other behavior-relevant features of the particle. Although these confounding issues may be of minimal concern for solid, smooth spheres, they can be of significance, for example, to droplets [which can be elongated to the shape of oblate spheroids when accelerated through a jet of an aerodynamic aerosol sizing instrument (Chen *et al.*, 1990)], or to fibers [which can be preferentially oriented in a jet or electric field in a manner that alters their mobility compared to their behavior in a normal airborne state (Chen *et al.*, 1993; Hoover *et al.*, 1989a)]. As shown by Ku and Kulkarni (2015) solid nanomaterials such as solid silver particles or gold nanorods have predictable relationships between aerodynamic and mobility diameter for a given aerosolization mechanism, but the determination of shape factors, electrical mobility behavior, and aerodynamic behavior for airborne nanomaterials of fibrous or agglomerate morphologies is of special interest for particles sizes in the transition region where both aerodynamic and thermodynamic factors influence particle behavior, and can affect estimates of aerodynamic and mobility diameter by factors of two to four.

The slip correction factor, which is large for very small particles, accounts for the ability of very small particles to "slip" between the air molecules without being impacted and thereby traverse greater distances. The value of the slip correction factor is ~236 for spherical particles of 1 nm diameter, decreases to a value of 5.4 for 50 nm diameter particles, further decreases to a value of 1.4 for particles of diameter 500 nm, and has a value of essentially one for micrometer- and larger-sized particles.

Determining an appropriate particle density can be difficult for particles that are porous or aggregates. The effective density of a cluster of particles can be much lower than the density of the individual particles themselves. When knowledge of effective particle density is needed to predict particle behavior, assumptions must be

made about the combination of particle shape and individual particle density. The work of Cena *et al*. (2014) provides an example of how measurements of metal oxide NP agglomerates from gas metal arc welding were used in conjunction with estimation of the effective particle density of the agglomerates to predict deposition in the respiratory tract. The authors estimated the size-dependent effective density of the welding fume agglomerates as a function of agglomerate particle size by applying the ratio of the density of carbon soot to the density of FeO in combination with the ratio of measured effective aerosol agglomerate density reported in Park *et al*. (2003). Miller *et al*. (2013) describe the estimation of human lung burdens based on individual particle density estimated from scanning electron microscopy and cascade impactor samples using the Multiple Path Particle Deposition Model (ARA, 2016). Additional details on the shape and slip correction factors can be found in Hinds (1999) and ICRP Publication 66 (ICRP, 1994a).

Aerodynamic diameter is the relevant characteristic of large particles and can be directly measured by sampling devices such as inertial impactors. Thermodynamic diameter is the relevant characteristic of small particles and can be directly measured by sampling devices such as diffusion batteries. Conversion of one diameter, including through the use of electron microscopic observations of particle-equivalent diameter, requires knowledge of density and appropriate assessment of particle shape. As shown in the upper panel of Figure C.3, thermodynamic diameter predicts particle behavior regardless of particle density for particles smaller than ~0.1 μm, while particle density must be known to correctly predict the particle behavior of larger particles. At the same time, as shown in the lower panel of Figure C.3, aerodynamic diameter predicts particle behavior regardless of particle density for particles larger than ~1 μm, while particle density must be known to correctly predict the particle behavior of smaller particles.

As illustrated in Figure C.3, the fraction of inhaled material deposited in the respiratory tract is the same, regardless of which type of diameter is used (ICRP, 1994a). In the upper plot involving thermodynamic diameter, the deposition fraction for a 1 nm diameter particle is essentially 100 %. Moving to the lower plot, if the particle had density 10 g cm^{-3} and shape factor one (*i.e*., d_{ae} = 10 nm) then the deposition fraction is, of course, once again, essentially 100 %.

Similar, equivalent results can be seen for the d_{th} = 50 nm and d_{ae} = 250 nm example, as well as for particles of any other size, as long as there is sufficient knowledge of: (1) the volume equivalent diameter, (2) the shape factor, and (3) the density.

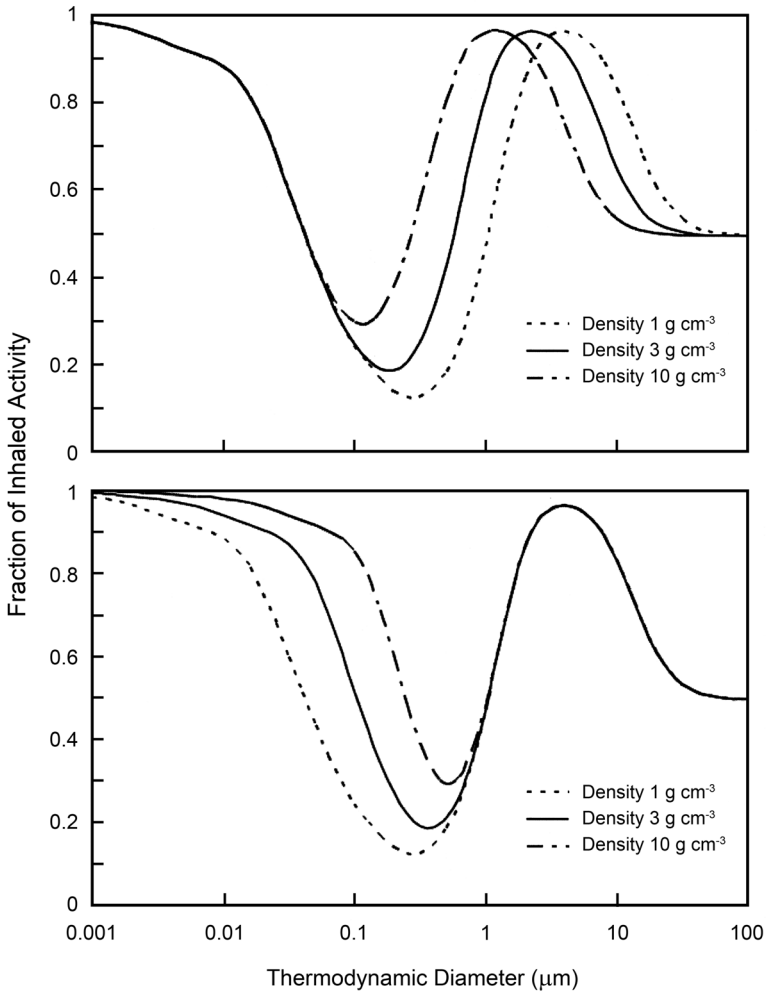


Fig. C.3. Comparison of total deposition in the human respiratory tract as a function of (upper) thermodynamic diameter and (lower) aerodynamic diameter (Hoover, 2010b; ICRP, 1994a).

C.5 Particle Size Distributions are Frequently Lognormal

Commonly encountered radioactive aerosols in the workplace have a lognormal size distribution (Esmen and Hammad, 1977) with some aerosols comprising mixtures of particle size distributions from different sources. Figure C.4 illustrates the lognormal aerosol particle distribution relationships among diameters of interest for aerosol characterization and aerosol behavior.

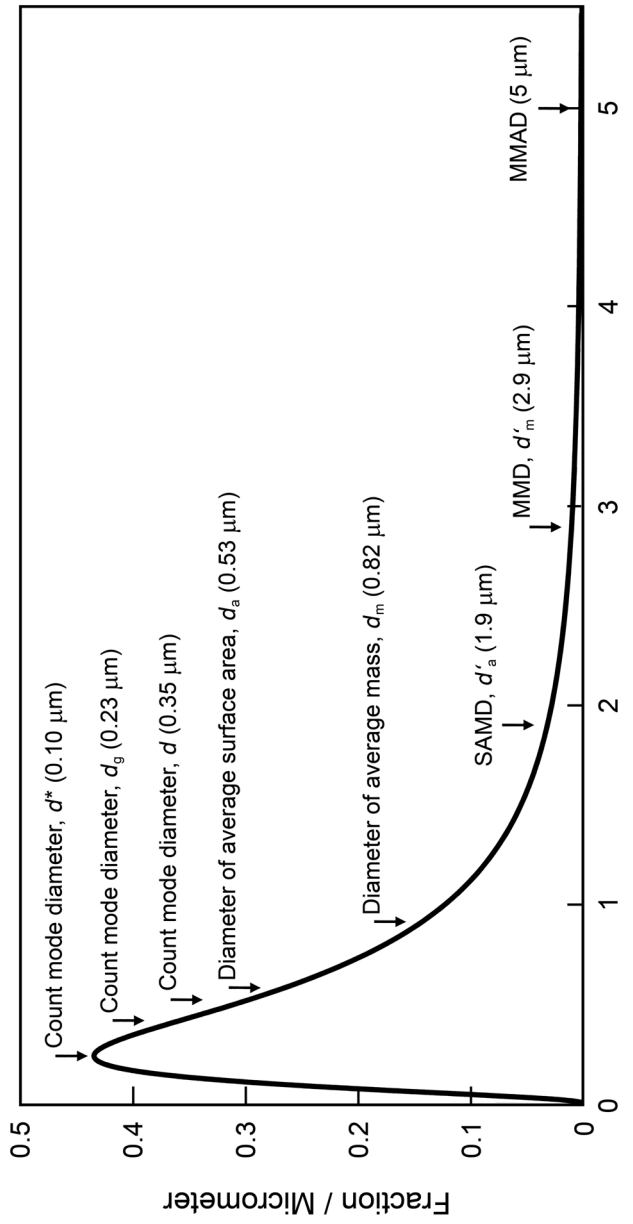


Fig. C.4. Illustration of the lognormal aerosol particle distribution relationships among diameters of interest for aerosol characterization and aerosol behavior (adapted from Hoover, 2010b) (CMD = count median diameter, MMD = mass median diameter, SAMD = surface area median diameter).

In this example:

- count mode diameter (d^*) is 0.10 μm;
- count median diameter (d_g) is 0.23 μm;
- count mean diameter ($\bar{d}$) is 0.35 μm;
- diameter of average surface area (d_a) is 0.54 μm;
- diameter of average mass (d_m) is 0.82 μm;
- surface area median diameter (d'_a) is 1.9 μm;
- surface area mean diameter ($\bar{d}_a$) is 1.90 μm;
- mass median diameter (d'_m) is 2.9 μm; and
- mass median aerodynamic diameter is 5.0 μm.

Note that the mass median aerodynamic diameter and AMAD are the same for aerosols in which radioactivity is uniformly distributed with particle mass. Note also that while half of the airborne radioactivity is associated with particles larger than 5 μm aerodynamic diameter and half of the radioactivity is associated with particles smaller than 5 μm aerodynamic diameter, there are relatively few particles on a count basis in the larger size fraction.

C.6 Nanoparticles Dominate the Count Distribution

While larger particles dominate the mass distribution, NP dominate the count distribution. Figure C.5 illustrates the differences among the distribution of particle number (which is dominated by particles in the nano-size range), the distribution of particle surface (which involves the diameter-squared relationship of surface area), and the distribution of particle mass (which involves the diameter cubed relationship). The figure uses a logarithmic scale for the abscissa to show that the count, surface area, and mass distributions are normally distributed in log space. The particle size distribution illustrated in these figures is for spherical particles with AMAD 5 μm, geometric standard deviation 2.5, and particle density 3 g cm^{-3}. These distribution parameters for size, geometric standard deviation, and density are the reference values recommended by ICRP Publication 66 (ICRP, 1994a) for aerosols encountered in occupational exposure settings.

Table C.1 illustrates the relationship between aerosol mass, surface area and number count in the nano-size range. As the median diameter of the aerosol size distribution decreases, the fraction of particle mass, surface area, and number count in the nano-size range increases dramatically.

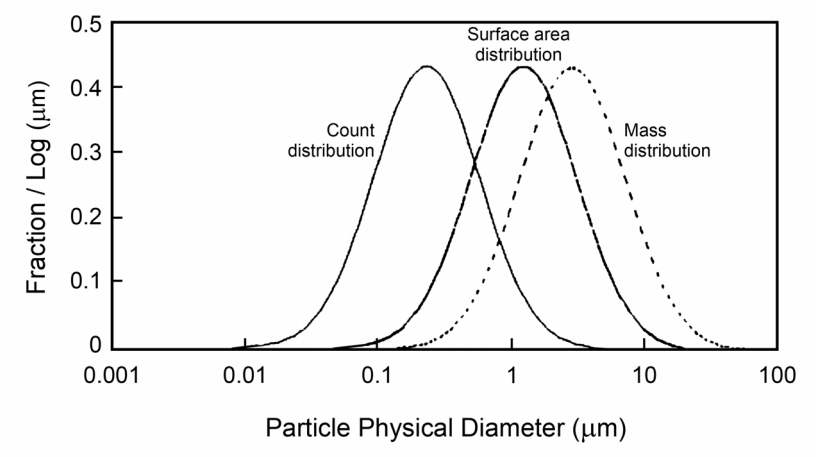


Fig. C.5. Comparison of the count, surface area and mass frequency distributions of an aerosol with a lognormal size distribution (Hoover, 2010b).

C.7 Nanoparticles Exist to Some Extent in the Majority of Occupational Aerosols

Figure C.6 illustrates that NP exist to some extent in most aerosols, even when the mass median aerodynamic diameter of the aerosol is large. Nearly 16 % of particles in the AMAD 5 μm default ICRP workplace aerosol distribution have particle physical diameters in the nano-size range (*i.e.*, in the size range smaller than 100 nm). Note also that "percent less than stated size" is linearly related to particle count, particle surface area and particle mass when particle size is lognormally distributed. The red line delineates the median values. The green line delineates the count fraction with physical diameter <100 nm.

C.8 Smaller Particles have a Greater Fraction of Their Atoms at the Particle Surface

Table C.2 presents an example of information from Smith *et al*. (1977) about the theoretical relationships among particle size, total number of plutonium atoms per particle, and the percent of plutonium atoms at the particle surface, for particles assumed to be round, smooth spheres. It can be seen that material in smaller particles might be considered more biologically accessible per unit mass than material of a larger particle size deposited in the lung in an equal amount of mass. Note that as discussed previously, the ICRP (1994a) HRTM treats particle size (as it influences deposition

TABLE C.1—*Fraction of aerosol mass, surface area, and number count in the nano-size range (d < 100 nm) for a range of particle size distributions (adapted from Cash, 2014).*

AMAD[a] and/or MMD[b] (μm)	SAMD[c] (μm)	CMD[d] (μm)	Fraction of Mass in Particles with $d < 100$ nm	Fraction of Surface Area in Particles with $d < 100$ nm	Fraction of Count in Particles with $d < 100$ nm
AMAD 5 μm – ICRP default workplace size distribution = MMD 2.9 μm	1.9	0.23	0.00001	0.0007	0.16
AMAD 1 μm – ICRP default environmental size distribution = MMD 0.6 μm	0.4	0.047	0.006	0.07	0.8
MMD 0.5 μm	0.3	0.04	0.04	0.1	0.84
MMD 0.1 μm	0.07	0.008	0.5	0.68	0.997
MMD 0.05 μm	0.03	0.004	0.78	0.89	0.9999
MMD 0.01 μm	0.007	0.0008	0.99	0.999	0.9999999

[a]AMAD = activity median aerodynamic diameter
[b]MMD = mass median diameter
[c]SAMD = surface area median diameter
[d]CMD = count median diameter

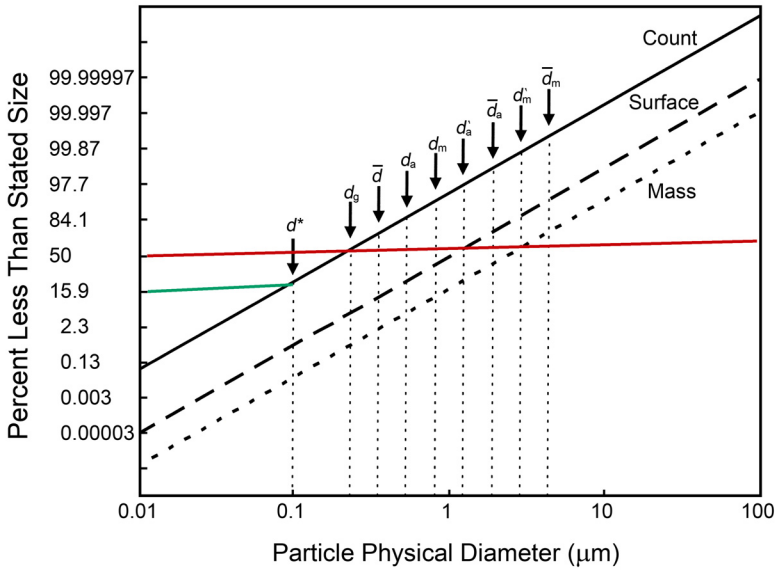


Fig. C.6. Log-probability plot illustrating the relationships among diameters for a log-normally distributed aerosol with ICRP default properties AMAD 5 μm, geometric standard deviation 2.5 and density 3 g cm^{-3} (Hoover, 2010b).

TABLE C.2—*Theoretical relationship among $^{239}PuO_2$ particle size, total number of plutonium atoms per particle, and the number and percent of plutonium atoms at the particle surface for spherical particles of faced-centered cubic crystalline material with a lattice constant of 0.54 nm (adapted from Smith et al., 1977).*

Particle Diameter (nm)	Total Number of Plutonium Atoms	Number of Plutonium Atoms at Surface	Percent of Plutonium Atoms at Surface
1	24.1	21.5	89
2	149	86	58
3	456	194	43
5	1,932	538	28
10	14,367	2,152	15
25	2.1×10^5	1.3×10^4	6
50	1.7×10^6	5.4×10^4	3
100	1.3×10^7	2.1×10^5	2

in the respiratory tract) separately from solubility class (*i.e.*, fast, medium, or slow as it describes the transfer of material from lung to blood and other organs and tissues). Keeping the parameters separate recognizes that the intrinsic dissolution behavior of a material may vary as a function of particle size. A more ideal approach might be to establish mechanistically realistic relationships between particle size and particle-surface-proportional dissolution so that determination of the characteristic dissolution behavior of a material could be used to scale biological transfer as a function of the primary particle size and the degree of agglomeration.

C.9 Number Concentrations of Concern Depend on the Material of Concern

Table C.3 illustrates how the airborne number concentrations of concern depend on the inherent toxicity of a material of concern. For example, because of its shorter half-life and therefore higher rate of alpha-particle emission, ^{238}Pu presents a higher hazard per unit particle mass than ^{239}Pu and other hazardous nuclear-related materials such as uranium and beryllium. (Given that the mass of an individual particle is on the order of a picogram, then ~10^{12} particles are associated with a gram of mass, and billions of particles are associated with micrograms of mass.) However, because the radioactivity concentrations of concern for a highly radioactive material such as ^{238}Pu may only involve a few particles per cubic meter, high air-sampling rates may be required to collect such particles in a statistically reliable manner (Scott and Fencl, 1999; Scott *et al.*,1997). Thus, if individuals must be protected from inhaling only a few particles, then airborne concentrations should be kept low by engineering controls, or (as a last resort) by respiratory protection having an appropriately high APF. Note that the Table C.3 values involve the useful health physics concept of the DAC, which is the concentration to which a worker can be exposed for a work year of 2,000 h, with a breathing rate of 20 L min^{-1}, without exceeding an annual limit on intake for that radionuclide that would result in a radiation dose equal to the U.S. statutory limit of 50 mSv (5 rem).

C.10 Realistic Airborne Particle Number Concentrations can be Limited by Coagulation

Figure C.7 illustrates the temporal decrease in airborne PNC that results from the tendency of particles to coagulate. As shown in the figure, concentrations >10^{12} particles per cm^3 can only exist for a few microseconds, concentrations >10^{10} particles per cm^3 cannot persist longer than about a second, and concentrations >10^8 particles per cm^3 can only last about a minute. However, particle

TABLE C.3—*Number of particles per cubic meter as a function of monodisperse particle size for selected toxic materials at their DAC (adapted from Hoover, 2010c).*

Physical Particle Diameter (μm)	$^{238}PuO_2$[a]	$^{239}PuO_2$[b]	Enriched Uranium[c]	Beryllium Metal[d]
10	0.0001	0.02	54	1,900
5	0.0008	0.15	430	15,000
3	0.004	0.7	2,000	71,000
1	0.1	20	54,000	1,900,000
0.5	0.8	150	430,000	15,000,000
0.3	4	700	2,000,000	71,000,000
0.1	100	2,000	54,000,000	2×10^9
0.05	800	150,000	430,000,000	1.5×10^{10}
0.03	4,000	700,000	2×10^9	7×10^{10}
0.01	100,000	2,000,000	5×10^{10}	2×10^{12}
0.005	800,000	150,000,000	4×10^{11}	1.5×10^{13}
0.003	4,000,000	700,000,000	2×10^{12}	7×10^{13}
0.001	100,000,000	2×10^9	5×10^{13}	2×10^{15}

[a]Insoluble ^{238}Pu has a specific activity of 6.44×10^{11} Bq g^{-1} and a DAC of 0.3 Bq m^{-3}.

[b]Insoluble ^{239}Pu has a specific activity of 2.26×10^9 Bq g^{-1} and a DAC of 0.2 Bq m^{-3}.

[c]For 93 % enriched uranium, the specific activity is 2.35×10^6 Bq g^{-1} (dominated by the contribution from ^{234}U, which is present at 1 % by mass), and the DAC is 0.6 Bq m^{-3}.

[d]The effective density of beryllium metal aerosol particles with a slight oxide coating is 2 g cm^{-3} (Hoover *et al.*, 1989b) and the occupational exposure limit for beryllium is 2 μg m^{-3}.

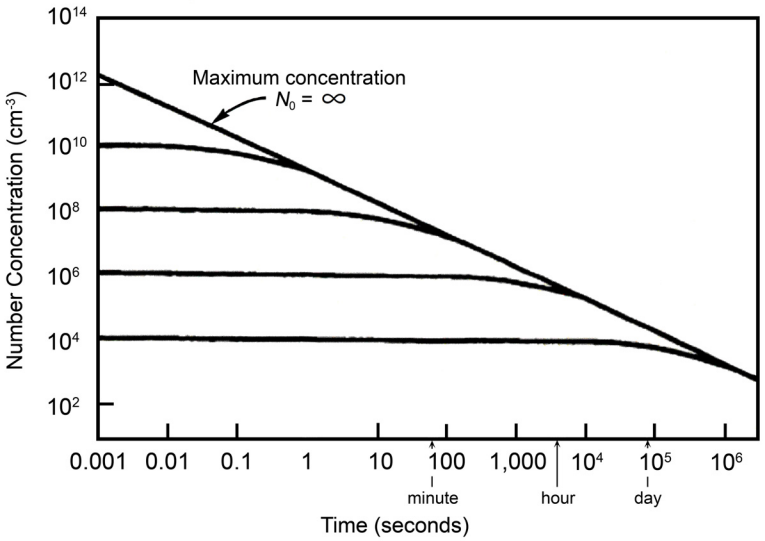


Fig. C.7. Illustration of temporal changes in PNCs due to simple monodisperse coagulation (adapted from Hinds, 1999). The data shown are for particles with a coagulation coefficient of 5×10^{-16} m^3 s^{-1}, which corresponds approximately to particles with physical diameters of either 2 or 200 nm.

concentrations on the order of 10^6 particles per cm^3 can remain for up to an hour, while concentrations of 10^4 particles per cm^3 and below can endure for days. Thus, as potential concentration-related scenarios are considered for occupational or environmental exposures, it is necessary to determine whether those scenarios are realistic, given that coagulation will be occurring. Note in Table C.3 that except for the 1 nm beryllium example, the particle concentration corresponding to the DAC for the various materials are in the range that can be sustained for more than about a minute. However, if a radioactive material of interest were present as a mixture with other materials (*i.e.*, with a proportionally lower radioactivity per unit mass) then coagulation could be a limiting factor in actual situations of aerosol formation and related human exposure.

The data shown in the Figure C.7 example are for particles with a coagulation coefficient of 5×10^{-16} m^3 s^{-1}. This value of the coagulation is associated with particles having physical diameters of ~2 or 200 nm. For particles with diameters between 2 and 200 nm, the value of the coagulation coefficient increases slightly to a maximum value of 1.15×10^{-15} m^3 s^{-1}, which corresponds to a physical diameter ~20 nm. Particles smaller than ~2 nm and particles

larger than 200 nm have lower coagulation coefficient values ranging down to ~3×10^{-16} m^3 s^{-1}.

C.11 Smaller Particles are More Difficult to Dislodge from Surfaces than Larger Particles

Hinds (1999) presents a comprehensive discussion of the ability of various forces to detach particles from surfaces. As shown in Table C.4, even for relatively large particles with physical diameter 100 μm, the value of 10^{-5} N for the adhesive force (*i.e.*, van der Waals force) is nearly two orders of magnitude greater than the value of 6×10^{-7} N for the gravitational force, and nearly four orders of magnitude greater than the value of 5×10^{-9} for the force of a typical workplace air current of 10 m s^{-1}. And as further shown in the table, it becomes increasingly more difficult to dislodge even smaller particles from surfaces. This does not mean that thick layers of dust cannot be disrupted and dispersed from surfaces as agglomerates of particles. As discussed in Section C.3, once airborne, dislodged materials will be dispersed by air currents and will settle from the air according to their particle size and the magnitude of the air current. The magnitudes and detailed natures of interactions between NP and surfaces and among NP in an agglomerated form are not yet fully understood. Batista *et al*. (2015) noted the challenges of assessing the influences of electrostatic, van der Waals, hydrophobic, and other interactions at the nanoscale, which may not be nonadditive.

TABLE C.4—*Comparison of adhesive, gravitational, and air current forces on spherical particles of standard density (adapted from Hinds, 1999).*

Particle Diameter (μm)	Force (N)		
	Adhesion[a]	Gravity	Air Current (at 10 m s^{-1})
0.1	10^{-8}	5×10^{-18}	2×10^{-10}
1.0	10^{-7}	5×10^{-15}	2×10^{-9}
10	10^{-6}	5×10^{-12}	3×10^{-8}
100	10^{-5}	5×10^{-9}	6×10^{-7}

[a]As calculated in Hinds (1999) for the condition of 50 % relative humidity by the equation from Corn (1961): Fadh = 0.063 d [1 + 0.009 (%RH)], where Fadh is the force in newtons, d is the particle diameter in meters, and %RH is the relative humidity in percent.

Abbreviations, Acronyms and Symbols

ABB	air-blood barrier
AI	alveolar-interstitial (region)
ALARA	as low as reasonably achievable (principle)
AMAD	activity median aerodynamic diameter
APF	assigned protection factor
bb	bronchiolar region
BB	bronchial region
CDG	Clinical Decision Guide
CED	committed effective dose
CNF	carbon nanofiber(s)
CNT	carbon nanotube(s)
DAC	derived air concentration
d_{ae}	aerodynamic equivalent diameter
d_e	volume-equivalent diameter
d_{th}	thermodynamic diameter
DTPA	diethylenetriamine pentaacetic acid
DU	depleted uranium
EC	elemental carbon
ELPI®	Electrical Low Pressure Impactor® (Dekati Ltd., Kangasala, Finland)
ENP	engineered nanoparticle(s)
ET_1	extra-thoracic region 1; comprising the nonciliated nasal airways
ET_2	extra thoracic region 2; comprising the ciliated nasal airways plus oral cavity and pharynx
FFR	filtering face-piece respirator
GI	gastrointestinal
GNP	gold nanoparticle(s)
HAT	human alimentary tract
HATM	Human Alimentary Tract Model (International Commission on Radiological Protection)
HEPA	high-efficiency particulate air (filter)
HRTM	Human Respiratory Tract Model
ID	injected dose
LEV	local exhaust ventilation

MPPS	most penetrating particle size
MWCNT	multi-walled carbon nanotube(s)
nanoMOUDI®	nano Multiple Orifice Uniform Deposit Impactor® (MSP Corporation, Shoreview, Minnesota)
NP	nanoparticle(s)
PM	particulate matter
PNC	particle number concentration(s)
PPE	personal protective equipment
Pu-M	plutonium citrate
Pu-P	polymeric plutonium
REL	recommended exposure limit (National Institute for Occupational Safety and Health)
RNP	radioactive nanoparticle(s)
RPE	respiratory protective equipment
SWCNT	single-walled carbon nanotube(s)

Glossary

absorption: The fractional passage of material (*e.g.*, a radionuclide) through a membrane, such as the fraction of intake that passes through the gut wall into the blood.

activity median aerodynamic diameter (AMAD**):** The diameter of a unit-density (1 g cm^{-3}) sphere with the same settling velocity in air as that of an aerosol particle whose activity is the median for the entire aerosol. Fifty percent of the activity (aerodynamically classified) in the aerosol is associated with particles greater than the AMAD. A log-normal distribution of particle sizes is usually assumed. Used when deposition depends principally on impaction and sedimentation. The default values for environmental (public) and occupational exposures are 1 μm and 5 μm, respectively.

assigned protection factor (APF**):** The minimum anticipated protection provided by a properly functioning respirator or class of respirators to a given percentage of properly fitted and trained users.

clearance: The action that results in the movement of radioactive material from the site of deposition in tissues and organs. This action can be natural, induced or enhanced by therapeutic means.

clearance classes: Prior to ICRP Publication 68 (ICRP, 1994b), clearance classes D (days), W (weeks), and Y (years) were used to provide an estimate of the retention timeframe of a particular radionuclide within the body. The revised approach to describing material behavior in the body now uses absorption types that are designated as Type F (fast), Type M (intermediate), or Type S (slow).

Clinical Decision Guide (CDG**):** An operational quantity introduced to guide physicians in making decisions in treatments to enhance decorporation of radionuclides deposited in the body. CDG is the maximum once-in-a-lifetime intake of a radionuclide that represents: (1) an acceptable stochastic risk, in the range of those associated with dose limits for emergency situations; and (2) avoidance of tissue reactions. A more detailed discussion of CDGs and a table of CDGs for specific radionuclides may be found in NCRP Report No. 161 (NCRP, 2009b).

colloid: Very fine solid particles that can remain suspended for long periods in water without settling, but which are incapable of passing through a semipermeable membrane.

corrective action: An action determined by an accident investigation to be the most appropriate to eliminate the cause of the incident or prevent the recurrence of the incident.

deposition: Any action resulting in the occurrence of radioactive material on or in external surfaces of the body or on or in internal tissues and organs.

dose: General term denoting the quantity of energy from ionizing radiation absorbed in a tissue or organ from either an external source or from radionuclides in the body. When unspecified, dose refers to the quantity of absorbed dose, measured in gray (1 Gy = 1 J kg^{-1}) or rad (1 rad = 100 ergs g^{-1}). Depending upon the context in which it is used, the generic term dose may also refer to equivalent dose, effective dose, or other dose-related quantities.

electrical mobility (equivalent) diameter: The diameter of a unit-density sphere having the same velocity in an electric field in air as the particle in question.

intake (radionuclides): The amount of radioactive material taken into the body by inhalation, absorption through the skin, ingestion, or through wounds. It is distinguished from *uptake*, which is the amount of material that eventually enters the systemic circulation, or *deposition*, which is the amount of the substance that is deposited in organs and tissues.

internal dose: Dose to organs or tissues of an organism due to intakes of radionuclides (*e.g.*, by ingestion, inhalation, through wounds, or dermal absorption).

nanocolloid: A group of nano-objects suspended in a liquid.

nanofiber: A nano-object with two external dimensions at the nanoscale.

nanomaterial: A larger matrix of nano-objects. The term is often used to describe engineered nano-objects, including engineered nanoparticles.

nano-object: A material with one, two or three external dimensions at the nanoscale.

nanoparticle (NP**):** A nano-object with all three external dimensions at the nanoscale.

nanoplatelets: A nano-object with one external dimension at the nanoscale.

nanorod: A solid nanofiber.

nanoscale: The size regime of objects that have one, two or three external dimensions in approximately the 1 to 100 nm size range.

nanotechnology: The manipulation of matter on a near-atomic scale (*i.e.*, nanoscale) to produce new structures, materials and devices.

nanotube: A hollow nanofiber.

radiation risk: The probability of a specified effect or response occurring following exposure to radiation.

radionuclide: An unstable (*i.e.*, radioactive) nuclide. A species of atom characterized by the constitution of its nucleus (*i.e.*, the number of protons and neutrons) and the excess energy available in the unstable nucleus.

secondary organs: Locations including liver, spleen, and bone marrow, to which materials may be translocated from their initial location of deposition in the body.

thermal rebound: An experimentally unsubstantiated phenomenon whereby very small nanoparticles that diffuse to the surface of filter media or other materials would have sufficient kinetic energy to escape surface adhesive forces (*e.g.*, van der Waals and electrostatic),

and thereby rebound from the surface in a manner similar to that of gas molecules, rather than remaining firmly attached to any surface they contact.

thermodynamic (diffusion equivalent) diameter: The diameter of a unit-density sphere having the same rate of diffusion in air as the particle in question.

Type F materials: Deposited materials that are readily absorbed into blood from the respiratory tract (fast rate of absorption).

Type M materials: Deposited materials that have intermediate rates of absorption into blood from the respiratory tract (moderate rate of absorption).

Type S materials: Deposited materials that are relatively insoluble in the respiratory tract (slow rate of absorption).

ultrafine particles: A term used in aerosol research to describe airborne particles smaller than 100 nm in diameter.

uptake: Quantity of a radionuclide taken up by the systemic circulation (*e.g.*, by injection into the blood, by absorption from compartments in the respiratory or gastrointestinal traces, or by absorption through the skin or through wounds in the skin).

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Scientific Committee and Staff

Mark D. Hoover (*Chairman*) is a senior research scientist in the Respiratory Health Division of the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention, in Morgantown, West Virginia. Dr. Hoover is coordinator of the NIOSH Exposure Assessment Cross-Sector Research Program, co-director of the NIOSH Center for Direct Reading and Sensor Technologies, and a critical area leader in the NIOSH Nanotechnology Research Center. NIOSH is the leading U.S. federal agency conducting research and making recommendations to prevent work-related illness, injury, disability and death. Prior to joining NIOSH in 2000, Dr. Hoover was an aerosol scientist for 25 y at the U.S. Department of Energy's Lovelace Respiratory Research Institute in Albuquerque, New Mexico. He earned a BS in mathematics and English in 1970 from Carnegie Mellon University and an MS and PhD in nuclear engineering in 1975 and 1980 from the University of New Mexico. Dr. Hoover is a certified health physicist, a certified industrial hygienist, and member and Fellow of the Health Physics Society, a member and Fellow of the American Association for Aerosol Research, and a member and Fellow of the American Industrial Hygiene Association. He has served as chairman or contributor to the development of many national and international standards; is the cofounder of the U.S. Air Monitoring Users Group; is a past chair of the AIHA Nanotechnology Working Group; and is chair of the HPS Nanotechnology Committee. Special emphasis areas for Dr. Hoover's work have included a graded approach to exposure assessment and characterization of nanoparticles in the workplace, development of a prototype *Nanoparticle Information Library*, and promotion of opportunities to apply performance-based occupational exposure limits or control banding approaches to nanotechnology. He co-edited the CRC Press handbook on *Radioactive Air Sampling Methods* and is lead editor for the monograph on *Nanoinformatics Principles and Practices*. Dr. Hoover has received a number of awards for scientific excellence and leadership including the Thomas T. Mercer Prize for Excellence in the

Field of Inhalable Materials and Medicinal Aerosols. Dr. Hoover has authored or co-authored more than 220 open literature publications.

David S. Myers (*Vice-Chairman*) received a BS in physics from Ripon College and an MPH in health physics from the University of Michigan under an AEC Fellowship. He was a health physicist at the Lawrence Livermore National Laboratory from 1965 to 2000 where he held various positions including Health Physics Group Leader and Radiation Safety Division Leader. Mr. Myers is a member and Fellow of the Health Physics Society and certified by the American Board of Health Physics. He has served on the American Board of Health Physics and as a director of the American Academy of Health Physics. David Myers served on the Council from 1996 to 2013 and has served on NCRP Scientific Committee 46 (now Program Area Committee 2) on operational health physics since 1988. He served as chairman of PAC 2 from 2006 to 2013.

Raymond A. Guilmette received a BS in nuclear engineering from Rensselaer Polytechnic Institute and an MS in environmental health sciences and a PhD in radiological health from New York University. For 40 y, he has studied the metabolism, biokinetics, dosimetry, and biological effects of internally deposited radionuclides; developed methods for removing radionuclides from the body (decorporation); and studied the mechanisms of deposition, clearance and retention of inhaled materials. Most of this research was performed at the Lovelace Respiratory Research Institute (LRRI) (formerly the Inhalation Toxicology Research Institute), where he worked for 28 y. From 2000 through 2007, he was team leader for internal dosimetry at the Los Alamos National Laboratory, assessing radiation doses for workers exposed to radionuclides associated with the nuclear weapons programs. In 2007, Dr. Guilmette returned to LRRI as Director of the Center for Countermeasures Against Radiation where he evaluated the efficacy of chemical compounds designed to decorporate radionuclides as well as drugs designed to ameliorate the effects of acute radiation syndrome from large external radiation doses. He is a past president of the Health Physics Society and the recipient of its Distinguished Scientific Achievement Award in 2002 and it's Evans Medal in 2015. Dr Guilmette, has given a number of honorary lectures, including the Newell Stannard Memorial Lecture in 2006; the G. William Morgan Lecture (HPS) in 2009, and the inaugural Patricia W. Durbin Memorial Lecture (Lawrence Berkeley National Laboratory) in 2010. He was a member of scientific committees of

the International Commission on Radiological Protection for 20 y, the chairman or member of several committees of NCRP (now a Distinguished Emeritus Member), and a member of committees of the International Agency for Research on Cancer, the U.S. Environmental Protection Agency, and the U.S. National Academies of Science. He currently is President of Ray Guilmette & Associates LLC.

Leigh J. Cash is a scientist in the Primary Physics and Design Group at Los Alamos National Laboratory (LANL). She is currently studying shock waves from hydrodynamic experiments and working to unify and advance the methods, applications and communication of uncertainties describing key performance and safety parameters of the U.S. nuclear stockpile. Her broader research interests are in exploring uncertainty communication, epistemic game theory, and the concepts of legitimacy, authority, and information as a strategic form of power. Dr. Cash completed a postdoctoral appointment in Statistics at LANL, has a DrPH from Johns Hopkins University, a MEM from Yale University, and a BSEH from the University of Georgia. She has also completed programs in Nuclear Law from the International School of Nuclear Law in Montpellier, France and in Negotiation and Leadership and Understanding Diplomacy and International Negotiations from the Program on Negotiation at the Harvard Law School. Her research and publications on the potential inhalation of ^{239}Pu and ^{238}Pu dioxide nanoparticles included the development and interpretation of absorption, dose and bioassay measurements; and implications of these findings for the broader and emerging area of radioactive nanomaterials in general. She is a member of the Acoustical Society of America, the American Bar Association, and the American Statistical Association.

Wolfgang G. Kreyling is a biophysicist recently retired from the Helmholtz Center Munich – German Research Center for Environmental Health (HMGU) where he coordinated all aerosol and engineered nanoparticle related research across five HMGU-institutes spanning research and development ranging from material sciences to toxicology and epidemiology. He additionally chaired the research and development program of the HMGU's Institute of Lung Biology and Disease on dosimetry of ultrafine aerosol particles and engineered nanoparticles in the respiratory tract and secondary target organs like the cardiovascular and the central nervous system. He currently serves as an external scientific advisor of the HMGU Institute of Epidemiology 2. His research interests range from

aerosol sciences and nanoparticle technology to biophysics of the lungs reaching from the particle characterization to dosimetry and nanoparticle lung interactions on the level of the entire organism, cells like alveolar macrophages, and molecular compounds. In 1985 Dr. Kreyling spent a sabbatical year in the Respiratory Biology Program at the Harvard School of Public Health, and that collaboration continues to this day. From 1999 until his retirement Dr. Kreyling also coordinated toxicological and epidemiological collaborations between the U.S. Environmental Protection Agency, National Health and Environmental Effects Research Laboratory, and HMGU on ambient air pollution research. In recent years he has been very much engaged with the International Society for Aerosols in Medicine, serving as its President from 2003 to 2005. He also served as a member of several expert panels of International, European and German committees. He is currently an associated editor of *Particle & Fibre Toxicology* as well as an editorial board member of several international particle-related journals. He has published more than 250 peer-reviewed articles and book chapters and reports of international panels. Dr. Kreyling has received a number of awards for scientific excellence and leadership including the Thomas T. Mercer Prize for Excellence in the Field of Inhalable Materials and Medicinal Aerosols. He was recently named a Highly Cited Researcher (2014 and 2015) and recognized as one of the world's leading scientific minds in toxicology.

Gunter Oberdorster is Professor Emeritus in the Department of Environmental Medicine at the University of Rochester, and has been the Director of the University of Rochester Ultrafine Particle Center, and Principle Investigator of a Multidisciplinary Research Initiative in Nanotoxicology. He serves currently as Director of the University of Rochester Inhalation Facility, advising faculty on the design of studies involving administration of particulate and gaseous materials to the respiratory tract of rodents by inhalation and by instillation or aspiration. He earned his DVM and PhD (Pharmacology) from the University of Giessen in Germany. He has served and continues to serve on many national and international committees and is recipient of several national and international scientific awards. He is on the editorial board of several scientific journals and serves as Associate Editor of *Environmental Health Perspectives*. For more than 35 y, Dr. Oberdorster has studied effects and underlying mechanisms of lung injury induced by inhaled materials of environmental and occupational relevance, including metals, polymers, ambient particulate, and gaseous pollutants. He specifically emphasizes the use of realistic exposures

and relevant doses to establish exposure-dose-response relationships in order to translate experimental results to human risk assessment through dosimetric extrapolation modeling. Results from his laboratory in the early 1990s were the first to point out the potential of ambient ultrafine particles to cause adverse effects, and to introduce the Ultrafine Particle Hypothesis. At the same time, he pointed out the propensity of nano-sized particles to travel from deposition sites in the respiratory tract to secondary organs by translocating across epithelial barriers to the blood and lymph circulation and along sensory nerves to the CNS. He proposed the importance of particle surface area and surface reactivity as most important dose metrics. His research on the smallest size of ambient airborne particles contributed to the emergence of the field of nanotoxicology due to the introduction of rapidly increasing nanotechnology and associated use of nanoparticles (<100 nm) in industry, consumer products and medicine, raising concerns about the potential toxicity of isometric, fibrous, and other shapes of nanoparticles when inhaled. Dr. Oberdorster's research continues to assess the correlation between physicochemical properties and effects of inhaled nano-particles on the pulmonary, vascular and central nervous systems, which is greatly enhanced by cross-disciplinary collaborative team work with local and international scientists. Dr. Oberdorster has received a number of awards for scientific excellence and leadership including the Thomas T. Mercer Prize for Excellence in the Field of Inhalable Materials and Medicinal Aerosols. Dr. Oberdorster has authored and co-authored over 300 publications related to environmental and occupational health, dosimetry, extrapolation modeling and risk assessment.

Rachel Smith was awarded a BSc in Physics and MSc in Radiation Physics by London University and PhD (Physics) by Surrey University and is a member of the U.K. Society for Radiological Protection. She has over 20 y of experience in radiation protection, particularly in the development of standards and the modeling of radionuclide transport in the environment. For the past 8 y she has been expanding her skills to address chemical hazards, including nanomaterials. She managed the development of the nanoparticle inhalation facility at the Public Health England Centre for Radiation, Chemical and Environmental Hazards and leads the cross-disciplinary Nanoparticle Inhalation Research Group. The current focus of the group's research is on the deposition, clearance and translocation of poorly soluble nanoparticles, using radioactively labeled nanomaterials. The group also has interests in the development of methodologies for the

characterization of nanoparticle aerosols and in the chemical and biophysical interactions between components of lung surfactant and nanoparticles. She is a member of the U.K. cross Government Nanotechnology Policy Officials Group and has contributed to a number of Organisation for Economic Co-operation and Development expert groups on toxicity testing for nanomaterials.

Michael P. Grissom (*Staff Consultant*) is a Technical Staff Consultant for NCRP and is the President of MPG-HP, Inc., Riverside, California a private consulting firm. He is a recognized authority on operational health physics issues, particularly related to radiation protection in management, military, reactor, medical, and accelerator operations. During 20 y of service in the U.S. Navy, Mr. Grissom served as a Radiation Safety/Laser Safety Officer (hospital) and provided Radiation Health Officer support to the Naval Radiological Controls Program (propulsion, industrial and weapons). Mr. Grissom conducted research in biophysics and radiobiological effects at the Armed Forces Radiobiology Research Institute, Bethesda, Maryland as a junior then senior scientist and served as the Director of Medical Records Search for the Navy Nuclear Test Personnel Review, Office of the Chief of Naval Operations, Washington, DC. Mr. Grissom provided support to the Effluent and Dose Assessment Group, Three Mile Island Unit 2 Recovery Team in 1979 to 1980. He has delivered numerous presentations at scientific and professional society meetings. In 2012, Mr. Grissom became a Fellow of the Health Physics Society (HPS). He previously received the HPS Volunteer Award for services associated with the Medical Health Physics Section and is a Past President of the HPS Accelerator Section. He also served in a number of positions for Stanford University over a period of 16 y at the Stanford Linear Accelerator Center National Accelerator Laboratory, Menlo Park, California including Department Head, Operational Health Physics, and Assistant Associate Director for Environment, Safety and Health.

The NCRP

The National Council on Radiation Protection and Measurements is a nonprofit corporation chartered by Congress in 1964 to:

1. Collect, analyze, develop and disseminate in the public interest information and recommendations about (a) protection against radiation and (b) radiation measurements, quantities and units, particularly those concerned with radiation protection.
2. Provide a means by which organizations concerned with the scientific and related aspects of radiation protection and of radiation quantities, units and measurements may cooperate for effective utilization of their combined resources, and to stimulate the work of such organizations.
3. Develop basic concepts about radiation quantities, units and measurements, about the application of these concepts, and about radiation protection.
4. Cooperate with the International Commission on Radiological Protection, the International Commission on Radiation Units and Measurements, and other national and international organizations, governmental and private, concerned with radiation quantities, units and measurements and with radiation protection.

The Council is the successor to the unincorporated association of scientists known as the National Committee on Radiation Protection and Measurements and was formed to carry on the work begun by the Committee in 1929.

The participants in the Council's work are the Council members and members of scientific and administrative committees. Council members are selected solely on the basis of their scientific expertise and serve as individuals, not as representatives of any particular organization. The scientific committees, composed of experts having detailed knowledge and competence in the particular area of the committee's interest, draft proposed recommendations. These are then submitted to the full membership of the Council for careful review and approval before being published.

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Lauriston S. Taylor Lectures

John W. Poston, Sr. (2016) *Radiation Protection and Regulatory Science*

Keith F. Eckerman (2015) *Dosimetry of Internal Emitters: Contributions of Radiation Protection Bodies and Radiological Events*

Fred A. Mettler, Jr. (2014) *On the Shoulders of Giants: Radiation Protection Over 50 Years*

John E. Till (2013) *When Does Risk Assessment Get Fuzzy?*

Antone L. Brooks (2012) *From the Field to the Laboratory and Back: The "What Ifs," "Wows," and "Who Cares" of Radiation Biology*

Eleanor A. Blakely (2011) *What Makes Particle Radiation so Effective?*

Charles E. Land (2010) *Radiation Protection and Public Policy in an Uncertain World*

John D. Boice, Jr. (2009) *Radiation Epidemiology: The Golden Age and Remaining Challenges*

Dade W. Moeller (2008) *Radiation Standards, Dose/Risk Assessments, Public Interactions, and Yucca Mountain: Thinking Outside the Box*

Patricia W. Durbin (2007) *The Quest for Therapeutic Actinide Chelators*

Robert L. Brent (2006) *Fifty Years of Scientific Research: The Importance of Scholarship and the Influence of Politics and Controversy*

John B. Little (2005) *Nontargeted Effects of Radiation: Implications for Low-Dose Exposures*

Abel J. Gonzalez (2004) *Radiation Protection in the Aftermath of a Terrorist Attack Involving Exposure to Ionizing Radiation*
Charles B. Meinhold (2003) *The Evolution of Radiation Protection: From Erythema to Genetic Risks to Risks of Cancer to ?*
R. Julian Preston (2002) *Developing Mechanistic Data for Incorporation into Cancer Risk Assessment: Old Problems and New Approaches*
Wesley L. Nyborg (2001) *Assuring the Safety of Medical Diagnostic Ultrasound*
S. James Adelstein (2000) *Administered Radioactivity: Unde Venimus Quoque Imus*
Naomi H. Harley (1999) *Back to Background*
Eric J. Hall (1998) *From Chimney Sweeps to Astronauts: Cancer Risks in the Workplace*
William J. Bair (1997) *Radionuclides in the Body: Meeting the Challenge!*
Seymour Abrahamson (1996) *70 Years of Radiation Genetics: Fruit Flies, Mice and Humans*
Albrecht Kellerer (1995) *Certainty and Uncertainty in Radiation Protection*
R.J. Michael Fry (1994) *Mice, Myths and Men*
Warren K. Sinclair (1993) *Science, Radiation Protection and the NCRP*
Edward W. Webster (1992) *Dose and Risk in Diagnostic Radiology: How Big? How Little?*
Victor P. Bond (1991) *When is a Dose Not a Dose?*
J. Newell Stannard (1990) *Radiation Protection and the Internal Emitter Saga*
Arthur C. Upton (1989) *Radiobiology and Radiation Protection: The Past Century and Prospects for the Future*
Bo Lindell (1988) *How Safe is Safe Enough?*
Seymour Jablon (1987) *How to be Quantitative about Radiation Risk Estimates*
Herman P. Schwan (1986) *Biological Effects of Non-ionizing Radiations: Cellular Properties and Interactions*
John H. Harley (1985) *Truth (and Beauty) in Radiation Measurement*
Harald H. Rossi (1984) *Limitation and Assessment in Radiation Protection*
Merril Eisenbud (1983) *The Human Environment—Past, Present and Future*
Eugene L. Saenger (1982) *Ethics, Trade-Offs and Medical Radiation*
James F. Crow (1981) *How Well Can We Assess Genetic Risk? Not Very*
Harold O. Wyckoff (1980) *From "Quantity of Radiation" and "Dose" to "Exposure" and "Absorbed Dose"—An Historical Review*
Hymer L. Friedell (1979) *Radiation Protection—Concepts and Trade Offs*
Sir Edward Pochin (1978) *Why be Quantitative about Radiation Risk Estimates?*
Herbert M. Parker (1977) *The Squares of the Natural Numbers in Radiation Protection*

Warren K. Sinclair Keynote Addresses

Richard E. Toohey (2016) *WARP: Where are the Radiation Professionals?*
Kenneth R. Kase (2015) *Influence of the NCRP on Radiation Protection in the United States: Guidance and Regulation*
Jerrold T. Bushberg (2014) *Science, Radiation Protection, and the NCRP: Building on the Past, Looking to the Future*
Shunichi Yamashita (2013) *Fukushima Nuclear Power Plant Accident and Comprehensive Health Risk Management*

Fred A. Mettler, Jr. (2012) *Childhood Exposure: An Issue from Computed Tomography Scans to Fukushima*
Marco Durante (2011) *Heavy Ions in Therapy and Space: Benefits and Risks*
Vincent T. Covello (2010) *Effective Risk Communication Before, During and After a Radiological Emergency: Challenges, Guidelines, Strategies and Tools*
Peter B. Lyons (2009) *The Role of a Strong Regulator in Safe and Secure Nuclear Energy*
Dudley T. Goodhead (2008) *Issues in Quantifying the Effects of Low-Level Radiation*
James A. Brink (2007) *Use and Misuse of Radiation in Medicine*
Mikhail Balonov (2006) *Retrospective Analysis of Impacts of the Chernobyl Accident*
B. John Garrick (2005) *Contemporary Issues in Risk-Informed Decision Making on Waste Disposition*
John W. Poston, Sr. (2004) *Current Challenges in Countering Radiological Terrorism*

Thomas S. Tenforde Topical Lectures

Jacques Lochard (2015) *Ethics and Radiation Protection*

Currently, the following committees are actively engaged in formulating recommendations:

Program Area Committee 1: Basic Criteria, Epidemiology, Radiobiology, and Risk
- SC 1-20 Biological Effectiveness of Photons as a Function of Energy
- SC 1-24 Radiation Exposures in Space and the Potential for Central Nervous System Effects
- SC 1-25 Recent Epidemiologic Studies and Implications for the Linear-Nonthreshold Model

Program Area Committee 2: Operational Radiation Safety
- SC 2-7 Radiation Safety of Sealed Radioactive Sources

Program Area Committee 3: Nuclear and Radiological Security and Safety
- SC 3-1 Guidance for Emergency Responder Dosimetry

Program Area Committee 4: Radiation Protection in Medicine
- SC 4-5 Radiation Protection in Dentistry Supplement: Cone Beam Computed Tomography, Digital Imaging and Handheld Dental Imaging
- SC 4-7 Evaluating and Communicating Radiation Risks for Studies Involving Human Subjects: Guidance for Researchers and Reviewing Bodies
- SC 4-8 Improving Patient Dose Utilization in Computed Tomography

Program Area Committee 5: Environmental Radiation and Radioactive Waste Issues
- SC 5-2 Radiation Protection for Naturally Occurring Radioactive Materials (NORM) and Technologically Enhanced NORM (TENORM) from Oil and Gas Recovery

Program Area Committee 6: Radiation Measurements and Dosimetry

SC 6-9 U.S. Radiation Workers and Nuclear Weapons Test Participants Radiation Dose Assessment

Program Area Committee 7: Radiation Education, Risk Communication, Outreach, and Policy

In recognition of its responsibility to facilitate and stimulate cooperation among organizations concerned with the scientific and related aspects of radiation protection and measurement, the Council has created a category of NCRP Collaborating Organizations. Organizations or groups of organizations that are national or international in scope and are concerned with scientific problems involving radiation quantities, units, measurements and effects, or radiation protection may be admitted to collaborating status by the Council. Collaborating Organizations provide a means by which NCRP can gain input into its activities from a wider segment of society. At the same time, the relationships with the Collaborating Organizations facilitate wider dissemination of information about the Council's activities, interests and concerns. Collaborating Organizations have the opportunity to comment on draft reports (at the time that these are submitted to the members of the Council). This is intended to capitalize on the fact that Collaborating Organizations are in an excellent position to both contribute to the identification of what needs to be treated in NCRP reports and to identify problems that might result from proposed recommendations. The present Collaborating Organizations with which NCRP maintains liaison are as follows:

American Academy of Dermatology
American Academy of Environmental Engineers
American Academy of Health Physics
American Academy of Orthopaedic Surgeons
American Association of Physicists in Medicine
American Brachytherapy Society
American College of Cardiology
American College of Medical Physics
American College of Nuclear Physicians
American College of Occupational and Environmental Medicine
American College of Radiology
American Conference of Governmental Industrial Hygienists
American Dental Association
American Industrial Hygiene Association
American Institute of Ultrasound in Medicine
American Medical Association
American Nuclear Society
American Pharmaceutical Association
American Podiatric Medical Association
American Public Health Association
American Radium Society
American Roentgen Ray Society
American Society for Radiation Oncology
American Society of Emergency Radiology
American Society of Health-System Pharmacists
American Society of Nuclear Cardiology
American Society of Radiologic Technologists

American Thyroid Association
Association of Educators in Imaging and Radiological Sciences
Association of University Radiologists
Bioelectromagnetics Society
Campus Radiation Safety Officers
College of American Pathologists
Conference of Radiation Control Program Directors, Inc.
Council on Radionuclides and Radiopharmaceuticals
Defense Threat Reduction Agency
Electric Power Research Institute
Federal Aviation Administration
Federal Communications Commission
Federal Emergency Management Agency
Genetics Society of America
Health Physics Society
Institute of Electrical and Electronics Engineers, Inc.
Institute of Nuclear Power Operations
International Brotherhood of Electrical Workers
International Society of Exposure Science
National Aeronautics and Space Administration
National Association of Environmental Professionals
National Center for Environmental Health/Agency for Toxic Substances
National Electrical Manufacturers Association
National Institute for Occupational Safety and Health
National Institute of Standards and Technology
Nuclear Energy Institute
Office of Science and Technology Policy
Paper, Allied-Industrial, Chemical and Energy Workers International Union
Product Stewardship Institute
Radiation Research Society
Radiological Society of North America
Society for Cardiovascular Angiography and Interventions
Society for Pediatric Radiology
Society for Risk Analysis
Society of Cardiovascular Computed Tomography
Society of Chairmen of Academic Radiology Departments
Society of Interventional Radiology
Society of Nuclear Medicine and Molecular Imaging
Society of Radiologists in Ultrasound
Society of Skeletal Radiology
U.S. Air Force
U.S. Army
U.S. Coast Guard
U.S. Department of Energy
U.S. Department of Housing and Urban Development
U.S. Department of Labor
U.S. Department of Transportation
U.S. Environmental Protection Agency
U.S. Navy

U.S. Nuclear Regulatory Commission
U.S. Public Health Service
Utility Workers Union of America

NCRP has found its relationships with these organizations to be extremely valuable to continued progress in its program.

Another aspect of the cooperative efforts of NCRP relates to the Special Liaison relationships established with various governmental organizations that have an interest in radiation protection and measurements. This liaison relationship provides: (1) an opportunity for participating organizations to designate an individual to provide liaison between the organization and NCRP; (2) that the individual designated will receive copies of draft NCRP reports (at the time that these are submitted to the members of the Council) with an invitation to comment, but not vote; and (3) that new NCRP efforts might be discussed with liaison individuals as appropriate, so that they might have an opportunity to make suggestions on new studies and related matters. The following organizations participate in the Special Liaison Program:

Australian Radiation Laboratory
Bundesamt fur Strahlenschutz (Germany)
Canadian Association of Medical Radiation Technologists
Canadian Nuclear Safety Commission
Central Laboratory for Radiological Protection (Poland)
China Institute for Radiation Protection
Commissariat a l'Energie Atomique (France)
Commonwealth Scientific Instrumentation Research Organization (Australia)
European Commission
Heads of the European Radiological Protection Competent Authorities
Health Council of the Netherlands
Health Protection Agency
International Commission on Non-Ionizing Radiation Protection
International Commission on Radiation Units and Measurements
International Commission on Radiological Protection
International Radiation Protection Association
Japanese Nuclear Safety Commission
Japan Radiation Council
Korea Institute of Nuclear Safety
Russian Scientific Commission on Radiation Protection
South African Forum for Radiation Protection
World Association of Nuclear Operators
World Health Organization, Radiation and Environmental Health

NCRP values highly the participation of these organizations in the Special Liaison Program.

The Council also benefits significantly from the relationships established pursuant to the Corporate Sponsor's Program. The program facilitates the interchange of information and ideas and corporate sponsors provide valuable fiscal support for the Council's program. This developing program currently includes the following Corporate Sponsors:

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The Council's activities have been made possible by the voluntary contribution of time and effort by its members and participants and the generous support of the following organizations:

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American College of Radiology
American College of Radiology Foundation
American Dental Association
American Healthcare Radiology Administrators
American Industrial Hygiene Association
American Insurance Services Group
American Medical Association
American Nuclear Society
American Osteopathic College of Radiology
American Podiatric Medical Association
American Public Health Association
American Radium Society
American Roentgen Ray Society
American Society for Radiation Oncology
American Society for Therapeutic Radiology and Oncology
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American Veterinary Medical Association
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Chem Nuclear Systems
Center for Devices and Radiological Health
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College of American Pathologists
Committee on Interagency Radiation Research and Policy Coordination
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EG&G Idaho, Inc.
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Florida Institute of Phosphate Research
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Global Dosimetry Solutions
Health Effects Research Foundation (Japan)
Health Physics Society
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Radiation Research Society
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Society of Pediatric Radiology
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NCRP Reports

No.	Title
8	*Control and Removal of Radioactive Contamination in Laboratories* (1951)
22	*Maximum Permissible Body Burdens and Maximum Permissible Concentrations of Radionuclides in Air and in Water for Occupational Exposure* (1959) [includes Addendum 1 issued in August 1963]
25	*Measurement of Absorbed Dose of Neutrons, and of Mixtures of Neutrons and Gamma Rays* (1961)
27	*Stopping Powers for Use with Cavity Chambers* (1961)
30	*Safe Handling of Radioactive Materials* (1964)
32	*Radiation Protection in Educational Institutions* (1966)
35	*Dental X-Ray Protection* (1970)
36	*Radiation Protection in Veterinary Medicine* (1970)
37	*Precautions in the Management of Patients Who Have Received Therapeutic Amounts of Radionuclides* (1970)
38	*Protection Against Neutron Radiation* (1971)
40	*Protection Against Radiation from Brachytherapy Sources* (1972)
41	*Specification of Gamma-Ray Brachytherapy Sources* (1974)
42	*Radiological Factors Affecting Decision-Making in a Nuclear Attack* (1974)
44	*Krypton-85 in the Atmosphere—Accumulation, Biological Significance, and Control Technology* (1975)
46	*Alpha-Emitting Particles in Lungs* (1975)
47	*Tritium Measurement Techniques* (1976)
49	*Structural Shielding Design and Evaluation for Medical Use of X Rays and Gamma Rays of Energies Up to 10 MeV* (1976)

50 *Environmental Radiation Measurements* (1976)
52 *Cesium-137 from the Environment to Man: Metabolism and Dose* (1977)
54 *Medical Radiation Exposure of Pregnant and Potentially Pregnant Women* (1977)
55 *Protection of the Thyroid Gland in the Event of Releases of Radioiodine* (1977)
57 *Instrumentation and Monitoring Methods for Radiation Protection* (1978)
58 *A Handbook of Radioactivity Measurements Procedures*, 2nd ed. (1985)
60 *Physical, Chemical, and Biological Properties of Radiocerium Relevant to Radiation Protection Guidelines* (1978)
61 *Radiation Safety Training Criteria for Industrial Radiography* (1978)
62 *Tritium in the Environment* (1979)
63 *Tritium and Other Radionuclide Labeled Organic Compounds Incorporated in Genetic Material* (1979)
64 *Influence of Dose and Its Distribution in Time on Dose-Response Relationships for Low-LET Radiations* (1980)
65 *Management of Persons Accidentally Contaminated with Radionuclides* (1980)
67 *Radiofrequency Electromagnetic Fields—Properties, Quantities and Units, Biophysical Interaction, and Measurements* (1981)
68 *Radiation Protection in Pediatric Radiology* (1981)
69 *Dosimetry of X-Ray and Gamma-Ray Beams for Radiation Therapy in the Energy Range 10 keV to 50 MeV* (1981)
70 *Nuclear Medicine—Factors Influencing the Choice and Use of Radionuclides in Diagnosis and Therapy* (1982)
72 *Radiation Protection and Measurement for Low-Voltage Neutron Generators* (1983)
73 *Protection in Nuclear Medicine and Ultrasound Diagnostic Procedures in Children* (1983)
74 *Biological Effects of Ultrasound: Mechanisms and Clinical Implications* (1983)
75 *Iodine-129: Evaluation of Releases from Nuclear Power Generation* (1983)
76 *Radiological Assessment: Predicting the Transport, Bioaccumulation, and Uptake by Man of Radionuclides Released to the Environment* (1984)
77 *Exposures from the Uranium Series with Emphasis on Radon and Its Daughters* (1984)
78 *Evaluation of Occupational and Environmental Exposures to Radon and Radon Daughters in the United States* (1984)
79 *Neutron Contamination from Medical Electron Accelerators* (1984)
80 *Induction of Thyroid Cancer by Ionizing Radiation* (1985)
81 *Carbon-14 in the Environment* (1985)
82 *SI Units in Radiation Protection and Measurements* (1985)
83 *The Experimental Basis for Absorbed-Dose Calculations in Medical Uses of Radionuclides* (1985)

84 *General Concepts for the Dosimetry of Internally Deposited Radionuclides* (1985)
86 *Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields* (1986)
87 *Use of Bioassay Procedures for Assessment of Internal Radionuclide Deposition* (1987)
88 *Radiation Alarms and Access Control Systems* (1986)
89 *Genetic Effects from Internally Deposited Radionuclides* (1987)
90 *Neptunium: Radiation Protection Guidelines* (1988)
92 *Public Radiation Exposure from Nuclear Power Generation in the United States* (1987)
93 *Ionizing Radiation Exposure of the Population of the United States* (1987)
94 *Exposure of the Population in the United States and Canada from Natural Background Radiation* (1987)
95 *Radiation Exposure of the U.S. Population from Consumer Products and Miscellaneous Sources* (1987)
96 *Comparative Carcinogenicity of Ionizing Radiation and Chemicals* (1989)
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99 *Quality Assurance for Diagnostic Imaging* (1988)
100 *Exposure of the U.S. Population from Diagnostic Medical Radiation* (1989)
101 *Exposure of the U.S. Population from Occupational Radiation* (1989)
102 *Medical X-Ray, Electron Beam and Gamma-Ray Protection for Energies Up to 50 MeV (Equipment Design, Performance and Use)* (1989)
103 *Control of Radon in Houses* (1989)
104 *The Relative Biological Effectiveness of Radiations of Different Quality* (1990)
105 *Radiation Protection for Medical and Allied Health Personnel* (1989)
106 *Limit for Exposure to "Hot Particles" on the Skin* (1989)
107 *Implementation of the Principle of As Low As Reasonably Achievable (ALARA) for Medical and Dental Personnel* (1990)
108 *Conceptual Basis for Calculations of Absorbed-Dose Distributions* (1991)
109 *Effects of Ionizing Radiation on Aquatic Organisms* (1991)
110 *Some Aspects of Strontium Radiobiology* (1991)
111 *Developing Radiation Emergency Plans for Academic, Medical or Industrial Facilities* (1991)
112 *Calibration of Survey Instruments Used in Radiation Protection for the Assessment of Ionizing Radiation Fields and Radioactive Surface Contamination* (1991)
113 *Exposure Criteria for Medical Diagnostic Ultrasound: I. Criteria Based on Thermal Mechanisms* (1992)
114 *Maintaining Radiation Protection Records* (1992)
115 *Risk Estimates for Radiation Protection* (1993)
116 *Limitation of Exposure to Ionizing Radiation* (1993)
117 *Research Needs for Radiation Protection* (1993)
118 *Radiation Protection in the Mineral Extraction Industry* (1993)

119 *A Practical Guide to the Determination of Human Exposure to Radiofrequency Fields* (1993)
120 *Dose Control at Nuclear Power Plants* (1994)
121 *Principles and Application of Collective Dose in Radiation Protection* (1995)
122 *Use of Personal Monitors to Estimate Effective Dose Equivalent and Effective Dose to Workers for External Exposure to Low-LET Radiation* (1995)
123 *Screening Models for Releases of Radionuclides to Atmosphere, Surface Water, and Ground* (1996)
124 *Sources and Magnitude of Occupational and Public Exposures from Nuclear Medicine Procedures* (1996)
125 *Deposition, Retention and Dosimetry of Inhaled Radioactive Substances* (1997)
126 *Uncertainties in Fatal Cancer Risk Estimates Used in Radiation Protection* (1997)
127 *Operational Radiation Safety Program* (1998)
128 *Radionuclide Exposure of the Embryo/Fetus* (1998)
129 *Recommended Screening Limits for Contaminated Surface Soil and Review of Factors Relevant to Site-Specific Studies* (1999)
130 *Biological Effects and Exposure Limits for "Hot Particles"* (1999)
131 *Scientific Basis for Evaluating the Risks to Populations from Space Applications of Plutonium* (2001)
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134 *Operational Radiation Safety Training* (2000)
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150 *Extrapolation of Radiation-Induced Cancer Risks from Nonhuman Experimental Systems to Humans* (2005)
151 *Structural Shielding Design and Evaluation for Megavoltage X- and Gamma-Ray Radiotherapy Facilities* (2005)
152 *Performance Assessment of Near-Surface Facilities for Disposal of Low-Level Radioactive Waste* (2005)
153 *Information Needed to Make Radiation Protection Recommendations for Space Missions Beyond Low-Earth Orbit* (2006)
154 *Cesium-137 in the Environment: Radioecology and Approaches to Assessment and Management* (2006)
155 *Management of Radionuclide Therapy Patients* (2006)
156 *Development of a Biokinetic Model for Radionuclide-Contaminated Wounds and Procedures for Their Assessment, Dosimetry and Treatment* (2006)
157 *Radiation Protection in Educational Institutions* (2007)
158 *Uncertainties in the Measurement and Dosimetry of External Radiation* (2007)
159 *Risk to the Thyroid from Ionizing Radiation* (2008)
160 *Ionizing Radiation Exposure of the Population of the United States* (2009)
161 *Management of Persons Contaminated with Radionuclides* (2008)
162 *Self Assessment of Radiation-Safety Programs* (2009)
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164 *Uncertainties in Internal Radiation Dose Assessment* (2009)
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Volume VIII. NCRP Report No. 58
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Volume XX. NCRP Reports Nos. 105, 106, 107, 108
Volume XXI. NCRP Reports Nos. 109, 110, 111
Volume XXII. NCRP Reports Nos. 112, 113, 114
Volume XXIII. NCRP Reports Nos. 115, 116, 117, 118
Volume XXIV. NCRP Reports Nos. 119, 120, 121, 122
Volume XXV. NCRP Report No. 123I and 123II
Volume XXVI. NCRP Reports Nos. 124, 125, 126, 127
Volume XXVII. NCRP Reports Nos. 128, 129, 130
Volume XXVIII. NCRP Reports Nos. 131, 132, 133
Volume XXIX. NCRP Reports Nos. 134, 135, 136, 137
Volume XXX. NCRP Reports Nos. 138, 139
Volume XXXI. NCRP Report No. 140
Volume XXXII. NCRP Reports Nos. 141, 142, 143
Volume XXXIII. NCRP Report No. 144
Volume XXXIV. NCRP Reports Nos. 145, 146, 147
Volume XXXV. NCRP Reports Nos. 148, 149
Volume XXXVI. NCRP Reports Nos. 150, 151, 152
Volume XXXVII, NCRP Reports Nos. 153, 154, 155
Volume XXXVIII, NCRP Reports Nos. 156, 157, 158
Volume XXXIX, NCRP Reports Nos. 159, 160
Volume XL. NCRP Report No. 161 (Vols. I and II)
Volume XLI. NCRP Reports Nos. 162, 163
Volume XLII. NCRP Reports Nos. 165, 166, 167
Volume XLIII. NCRP Reports Nos. 168, 169
Volume XLIV. NCRP Reports Nos. 170, 171
Volume XLV. NCRP Reports Nos. 172, 173

NCRP Commentaries

No.	Title
1	*Krypton-85 in the Atmosphere—With Specific Reference to the Public Health Significance of the Proposed Controlled Release at Three Mile Island* (1980)
4	*Guidelines for the Release of Waste Water from Nuclear Facilities with Special Reference to the Public Health Significance of the Proposed Release of Treated Waste Waters at Three Mile Island* (1987)
5	*Review of the Publication, Living Without Landfills* (1989)
6	*Radon Exposure of the U.S. Population—Status of the Problem (1991)*
7	*Misadministration of Radioactive Material in Medicine—Scientific Background* (1991)
8	*Uncertainty in NCRP Screening Models Relating to Atmospheric Transport, Deposition and Uptake by Humans* (1993)
9	*Considerations Regarding the Unintended Radiation Exposure of the Embryo, Fetus or Nursing Child* (1994)
10	*Advising the Public about Radiation Emergencies: A Document for Public Comment* (1994)
11	*Dose Limits for Individuals Who Receive Exposure from Radionuclide Therapy Patients* (1995)
12	*Radiation Exposure and High-Altitude Flight* (1995)
13	*An Introduction to Efficacy in Diagnostic Radiology and Nuclear Medicine (Justification of Medical Radiation Exposure)* (1995)
14	*A Guide for Uncertainty Analysis in Dose and Risk Assessments Related to Environmental Contamination* (1996)
15	*Evaluating the Reliability of Biokinetic and Dosimetric Models and Parameters Used to Assess Individual Doses for Risk Assessment Purposes* (1998)
16	*Screening of Humans for Security Purposes Using Ionizing Radiation Scanning Systems* (2003)
17	*Pulsed Fast Neutron Analysis System Used in Security Surveillance* (2003)
18	*Biological Effects of Modulated Radiofrequency Fields* (2003)
19	*Key Elements of Preparing Emergency Responders for Nuclear and Radiological Terrorism* (2005)
20	*Radiation Protection and Measurement Issues Related to Cargo Scanning with Accelerator-Produced High-Energy X Rays* (2007)
21	*Radiation Protection in the Application of Active Detection Technologies* (2011)
22	*Radiological Health Protection Issues Associated With Use of Active Detection Technology Systems for Detection of Radioactive Threat Materials* (2011)
23	*Radiation Protection for Space Activities: Supplement to Previous Recommendations* (2014)
24	*Health Effects of Low Doses of Radiation: Perspectives on Integrating Radiation Biology and Epidemiology* (2015)
25	*Potential for Central Nervous System Effects from Radiation Exposure During Space Activities Phase I: Overview* (2016)
26	*Guidance on Radiation Dose Limits for the Lens of the Eye* (2016)

Proceedings of the Annual Meeting

No.	Title
1	*Perceptions of Risk,* Proceedings of the Fifteenth Annual Meeting held on March 14-15, 1979 (including Taylor Lecture No. 3) (1980)
3	*Critical Issues in Setting Radiation Dose Limits*, Proceedings of the Seventeenth Annual Meeting held on April 8-9, 1981 (including Taylor Lecture No. 5) (1982)
4	*Radiation Protection and New Medical Diagnostic Approaches,* Proceedings of the Eighteenth Annual Meeting held on April 6-7, 1982 (including Taylor Lecture No. 6) (1983)
5	*Environmental Radioactivity,* Proceedings of the Nineteenth Annual Meeting held on April 6-7, 1983 (including Taylor Lecture No. 7) (1983)
6	*Some Issues Important in Developing Basic Radiation Protection Recommendations*, Proceedings of the Twentieth Annual Meeting held on April 4-5, 1984 (including Taylor Lecture No. 8) (1985)
7	*Radioactive Waste*, Proceedings of the Twenty-First Annual Meeting held on April 3-4, 1985 (including Taylor Lecture No. 9)(1986)
8	*Nonionizing Electromagnetic Radiations and Ultrasound,* Proceedings of the Twenty-Second Annual Meeting held on April 2-3, 1986 (including Taylor Lecture No. 10) (1988)
9	*New Dosimetry at Hiroshima and Nagasaki and Its Implications for Risk Estimates*, Proceedings of the Twenty-Third Annual Meeting held on April 8-9, 1987 (including Taylor Lecture No. 11) (1988)
10	*Radon*, Proceedings of the Twenty-Fourth Annual Meeting held on March 30-31, 1988 (including Taylor Lecture No. 12) (1989)
11	*Radiation Protection Today—The NCRP at Sixty Years*, Proceedings of the Twenty-Fifth Annual Meeting held on April 5-6, 1989 (including Taylor Lecture No. 13) (1990)
12	*Health and Ecological Implications of Radioactively Contaminated Environments*, Proceedings of the Twenty-Sixth Annual Meeting held on April 4-5, 1990 (including Taylor Lecture No. 14) (1991)
13	*Genes, Cancer and Radiation Protection,* Proceedings of the Twenty-Seventh Annual Meeting held on April 3-4, 1991 (including Taylor Lecture No. 15) (1992)
14	*Radiation Protection in Medicine,* Proceedings of the Twenty-Eighth Annual Meeting held on April 1-2, 1992 (including Taylor Lecture No. 16) (1993)
15	*Radiation Science and Societal Decision Making,* Proceedings of the Twenty-Ninth Annual Meeting held on April 7-8, 1993 (including Taylor Lecture No. 17) (1994)
16	*Extremely-Low-Frequency Electromagnetic Fields: Issues in Biological Effects and Public Health*, Proceedings of the Thirtieth Annual Meeting held on April 6-7, 1994 (not published).
17	*Environmental Dose Reconstruction and Risk Implications,* Proceedings of the Thirty-First Annual Meeting held on April 12-13, 1995 (including Taylor Lecture No. 19) (1996)
18	*Implications of New Data on Radiation Cancer Risk*, Proceedings of the Thirty-Second Annual Meeting held on April 3-4, 1996 (including Taylor Lecture No. 20) (1997)

19 *The Effects of Pre- and Postconception Exposure to Radiation*, Proceedings of the Thirty-Third Annual Meeting held on April 2-3, 1997, Teratology **59**, 181–317 (1999)

20 *Cosmic Radiation Exposure of Airline Crews, Passengers and Astronauts*, Proceedings of the Thirty-Fourth Annual Meeting held on April 1-2, 1998, Health Phys. **79**, 466–613 (2000)

21 *Radiation Protection in Medicine: Contemporary Issues*, Proceedings of the Thirty-Fifth Annual Meeting held on April 7-8, 1999 (including Taylor Lecture No. 23) (1999)

22 *Ionizing Radiation Science and Protection in the 21st Century*, Proceedings of the Thirty-Sixth Annual Meeting held on April 5-6, 2000, Health Phys. **80**, 317–402 (2001)

23 *Fallout from Atmospheric Nuclear Tests—Impact on Science and Society*, Proceedings of the Thirty-Seventh Annual Meeting held on April 4-5, 2001, Health Phys. **82**, 573–748 (2002)

24 *Where the New Biology Meets Epidemiology: Impact on Radiation Risk Estimates*, Proceedings of the Thirty-Eighth Annual Meeting held on April 10-11, 2002, Health Phys. **85**, 1–108 (2003)

25 *Radiation Protection at the Beginning of the 21st Century–A Look Forward*, Proceedings of the Thirty-Ninth Annual Meeting held on April 9–10, 2003, Health Phys. **87**, 237–319 (2004)

26 *Advances in Consequence Management for Radiological Terrorism Events*, Proceedings of the Fortieth Annual Meeting held on April 14–15, 2004, Health Phys. **89**, 415–588 (2005)

27 *Managing the Disposition of Low-Activity Radioactive Materials*, Proceedings of the Forty-First Annual Meeting held on March 30–31, 2005, Health Phys. **91**, 413–536 (2006)

28 *Chernobyl at Twenty*, Proceedings of the Forty-Second Annual Meeting held on April 3–4, 2006, Health Phys. **93**, 345–595 (2007)

29 *Advances in Radiation Protection in Medicine*, Proceedings of the Forty-Third Annual Meeting held on April 16-17, 2007, Health Phys. **95**, 461–686 (2008)

30 *Low Dose and Low Dose-Rate Radiation Effects and Models*, Proceedings of the Forty-Fourth Annual Meeting held on April 14–15, 2008, Health Phys. **97**, 373–541 (2009)

31 *Future of Nuclear Power Worldwide – Health, Safety, and Environment*, Proceedings of the Forty-Fifth Annual Meeting held on March 2–3, 2009, Health Phys. **100**(1), 2–112 (2011)

32 *Communication of Radiation Benefits and Risks in Decision Making*, Proceedings of the Forty-Sixth Annual Meeting held March 8–9, 2010, Health Phys. **101**(5), 497–629 (2011)

33 *Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions*, Proceedings of the Forty-Seventh Annual Meeting held on March 7–8, 2011, Health Phys. **103**(5), 529–684 (2012)

34 *Emerging Issues in Radiation Protection in Medicine, Emergency Response, and the Nuclear Fuel Cycle*, Proceedings of the Forty-Eighth Annual Meeting held March 12–13, 2012, Health Phys. **105**(5), 401–468 (2013)

35 *Radiation Dose the Impacts on Exposed Populations*, Proceedings of the Forty-Ninth Annual Meeting held March 11–12, 2013, Health Phys. **106**(2), 145–339 (2014)

36 *NCRP: Achievements of the Past 50 Years and Addressing the Needs of the Future*, Proceedings of the Fiftieth Annual Meeting held March 10–11, 2014, Health Phys. **108**(2), 97–293 (2015)

37 *Changing Regulations and Radiation Guidance: What Does the Future Hold?*, Proceedings of the Fifty-First Annual Meeting held March 16–17, 2015, Health Phys. **110**(2), 97–237 (2016)

38 *Meeting the Needs of the Nation for Radiation Protection*, Proceedings of the Fifty-Second Annual Meeting held April 11-12, 2016, Health Phys. **112**(2), 111–234 (2017)

Lauriston S. Taylor Lectures

No. Title

1 *The Squares of the Natural Numbers in Radiation Protection by* Herbert M. Parker (1977)

2 *Why be Quantitative about Radiation Risk Estimates?* by Sir Edward Pochin (1978)

3 *Radiation Protection—Concepts and Trade Offs* by Hymer L. Friedell (1979) [available also in *Perceptions of Risk*, see above]

4 *From "Quantity of Radiation" and "Dose" to "Exposure" and "Absorbed Dose"—An Historical Review* by Harold O. Wyckoff (1980)

5 *How Well Can We Assess Genetic Risk? Not Very* by James F. Crow (1981) [available also in *Critical Issues in Setting Radiation Dose Limits*, see above]

6 *Ethics, Trade-offs and Medical Radiation* by Eugene L. Saenger (1982) [available also in *Radiation Protection and New Medical Diagnostic Approaches*, see above]

7 *The Human Environment—Past, Present and Future* by Merril Eisenbud (1983) [available in *Environmental Radioactivity*, see above]

8 *Limitation and Assessment in Radiation Protection* by Harald H. Rossi (1984) [available also in *Some Issues Important in Developing Basic Radiation Protection Recommendations*, see above]

9 *Truth (and Beauty) in Radiation Measurement* by John H. Harley (1985) [available also in *Radioactive Waste*, see above]

10 *Biological Effects of Non-ionizing Radiations: Cellular Properties and Interactions* by Herman P. Schwan (1987) [available also in *Nonionizing Electromagnetic Radiations and Ultrasound*, see above]

11 *How to be Quantitative about Radiation Risk Estimates* by Seymour Jablon (1988) [available also in *New Dosimetry at Hiroshima and Nagasaki and its Implications for Risk Estimates*, see above]

12 *How Safe is Safe Enough?* by Bo Lindell (1988) [available also in *Radon*, see above]

13 *Radiobiology and Radiation Protection: The Past Century and Prospects for the Future* by Arthur C. Upton (1989) [available also in *Radiation Protection Today*, see above]

14 *Radiation Protection and the Internal Emitter Saga* by J. Newell Stannard (1990) [available also in *Health and Ecological Implications of Radioactively Contaminated Environments*, see above]
15 *When is a Dose Not a Dose?* by Victor P. Bond (1992) [available also in *Genes, Cancer and Radiation Protection*, see above]
16 *Dose and Risk in Diagnostic Radiology: How Big? How Little?* by Edward W. Webster (1992) [available also in *Radiation Protection in Medicine*, see above]
17 *Science, Radiation Protection and the NCRP* by Warren K. Sinclair (1993) [available also in *Radiation Science and Societal Decision Making,* see above]
18 *Mice, Myths and Men* by R.J. Michael Fry (1995)
19 *Certainty and Uncertainty in Radiation Research* by Albrecht M. Kellerer. Health Phys. **69**, 446–453 (1995)
20 *70 Years of Radiation Genetics: Fruit Flies, Mice and Humans* by Seymour Abrahamson. Health Phys. **71**, 624–633 (1996)
21 *Radionuclides in the Body: Meeting the Challenge* by William J. Bair. Health Phys. **73**, 423–432 (1997)
22 *From Chimney Sweeps to Astronauts: Cancer Risks in the Work Place* by Eric J. Hall. Health Phys. **75**, 357–366 (1998)
23 *Back to Background: Natural Radiation and Radioactivity Exposed* by Naomi H. Harley. Health Phys. **79**, 121–128 (2000)
24 *Administered Radioactivity: Unde Venimus Quoque Imus* by S. James Adelstein. Health Phys. **80**, 317–324 (2001)
25 *Assuring the Safety of Medical Diagnostic Ultrasound* by Wesley L. Nyborg. Health Phys. **82**, 578–587 (2002)
26 *Developing Mechanistic Data for Incorporation into Cancer and Genetic Risk Assessments: Old Problems and New Approaches* by R. Julian Preston. Health Phys. **85**, 4–12 (2003)
27 *The Evolution of Radiation Protection–From Erythema to Genetic Risks to Risks of Cancer to ?* by Charles B. Meinhold, Health Phys. **87**, 240–248 (2004)
28 *Radiation Protection in the Aftermath of a Terrorist Attack Involving Exposure to Ionizing Radiation* by Abel J. Gonzalez, Health Phys. **89**, 418–446 (2005)
29 *Nontargeted Effects of Radiation: Implications for Low Dose Exposures* by John B. Little, Health Phys. **91**, 416–426 (2006)
30 *Fifty Years of Scientific Research: The Importance of Scholarship and the Influence of Politics and Controversy* by Robert L. Brent, Health Phys. **93**, 348–379 (2007)
31 *The Quest for Therapeutic Actinide Chelators* by Patricia W. Durbin, Health Phys. **95**, 465–492 (2008)
32 *Yucca Mountain Radiation Standards, Dose/Risk Assessments, Thinking Outside the Box, Evaluations, and Recommendations* by Dade W. Moeller, Health Phys. **97**, 376–391 (2009)
33 *Radiation Epidemiology-the Golden Age and Future Challenges* by John D. Boice, Jr., Health Phys. **100**(1), 59–76 (2011)
34 *Radiation Protection and Public Policy in an Uncertain World* by Charles E. Land, Health Phys. **101**(5), 499–508 (2011)

35 *What Makes Particle Radiation so Effective?* by Eleanor A. Blakely, Health Phys. **103**(5), 508–528 (2012)
36 *From the Field to the Laboratory and Back: The What Ifs, Wows, and Who Cares of Radiation Biology*, by Antone L. Brooks, Health Phys. **105**(5), 407–421 (2013)
37 *When Does Risk Assessment Get Fuzzy?*, by John E. Till, Health Phys. **106**(2), 148-161 (2014)
38 *On the Shoulders of Giants—Radiation Protection Over 50 Years*, by Fred A. Mettler, Jr., Health Phys. **108**(2), 102–110 (2015)
39 *Dosimetry of Internal Emitters: Contributions of Radiation Protection Bodies and Radiological Events*, by Keith F. Eckerman, Health Phys. **110**(2), 192–200 (2016)
40 *Radiation Protection and Regulatory Science*, by John W. Poston, Sr., Health Phys. **112**(2), 193–198 (2017)

Warren K. Sinclair Keynote Addresses

No. Title

1 *Current Challenges in Countering Radiological Terrorism*, John W. Poston, Sr., Health Phys. **89**(5), 450–456 (2005)
2 *Contemporary Issues in Risk-Informed Decision Making on Waste Disposition*, B. John Garrick, Health Phys. **91**(5), 430–438 (2006)
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