DISSOLUTION AND PARTICLE SIZE CHARACTERIZATION
OF RADIOACTIVE CONTAMINANTS IN HANFORD FACILITIES:
CRITERIA FOR METHODS OF MEASUREMENT

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ABSTRACT

The purpose of this document is to discuss experimental methods that can be applied to evaluate the rate at which an actinide material is likely to dissolve in biological fluids. Criteria are recommended for the design and conduct of meaningful experimental procedures to sample a representative size fraction of the source material, to measure the rate of radionuclide dissolution, and to apply the results to assign the material to an appropriate ICRP Publication-30 lung retention class (or mixture of classes).

SUMMARY

Human exposure to an airborne radioactive contaminant results in a distribution of radiation dose to the lungs and other organs of the body which depends on many factors. The three most important factors are size distribution of the inhaled aerosol particles, solubility of the radioactive material in the lung or gut (gastrointestinal [GI] tract), and metabolism of the radionuclide in the tissues where it is retained. Inhaled particles deposit in regions of the respiratory tract according to their aerodynamic size. Once deposited, the pathways and rates of clearance of the radioactive contaminant material depend on the rate of dissolution of the particles, or on the rate at which radionuclides are leached from the particles. Dissolved material is transferred to the blood and translocated to other organs of the body, and eventually excreted. Radionuclides that are not dissolved from particles may eventually be cleared by a biomechanical mechanism such as mucociliary transport or phagocytic cell transport. Some of the particles deposited in the airways are retained in lung tissue or pulmonary lymph nodes for a length of time that depends on the material's rate of dissolution. For dose assessment purposes, these complex processes are represented by a compartment model of aerosol deposition and clearance recommended by the International Commission on Radiological Protection (ICRP) in Publication 30.

The ICRP Publication 30 (ICRP 30) recommends that radionuclides of defined chemical form be assigned to one of three classes of pulmonary retention. For actinide materials, however, well-defined, simple chemical forms are rarely encountered in practice, and it is necessary to exercise judgement in assigning a given material to an ICRP-30 retention class. The main purpose of this document is to discuss experimental methods that can be applied to evaluate the rate at which an actinide material of radiological concern is likely to dissolve in biological fluids. The document recommends criteria for the design and conduct of meaningful experimental procedures to sample a representative size fraction of the source material, to measure the rate of radionuclide dissolution, and to apply the results to assign the material to an appropriate ICRP-30 retention class.

Dissolution is best measured in two simulated biological fluids: gastric juice and lung fluid. Particles deposited in the upper respiratory tract, and

some of those from the lower respiratory tract, are cleared to the pharynx and swallowed to the stomach. Dissolution in simulated gastric juice provides a measure of absorption from the gut to blood (uptake factor, f_1) and a basis for determining the length of time needed to measure the slower dissolution rate that is likely to occur in simulated lung fluid. Experimental measurements follow the same procedures for both of the simulated biological fluids. The dissolution cell, and all materials in contact with the fluid, must be chemically inert and maintained under biologically sterile conditions to avoid artifacts. The chemical environment must be similar in nature to that *in vivo*. This environment is simulated using a fluid of similar chemical composition to the biological fluid, and a dissolution cell maintained at body temperature in which dissolved material is constantly cleared away from the surface of particles by continuous motion of the fluid. Aliquots of fluid are withdrawn from the cell on a schedule determined by the estimated dissolution rate of the material. Each aliquot is replaced with fresh fluid to keep the solution well below the point of saturation. At the end of a test, the remaining material is analyzed to determine the proportion of the sample dissolved in the aliquots. These results are evaluated in terms of a half-time of dissolution for the main component of the material, or, if necessary, for the half-time of each component of a mixture.

Measurement of the particle size distribution of a contaminant material has two roles in dose assessment: determining regional deposition in the respiratory tract, and qualitative consideration of the total surface area presented for dissolution. Methods for obtaining representative samples of the inhalable particle size distribution are discussed. Particle collection by a size-selective sampler mimics the *in vivo* deposition of an inhaled contaminant material. This eliminates the need for separate measurement and interpretation of the size distribution of particles that have been collected in a non-selective manner. Particles collected in the respirable size fraction provide a realistic sample to measure the dissolution rate of material that would actually be deposited in the pulmonary region of the lung. The larger particles in the coarse part of the inhalable fraction represent the particles deposited in the upper airways. These particles can also be used for dissolution rate measurement in simulated gastric juice to accurately estimate the fraction f_1 absorbed from the gut.

Material collected after an exposure incident, or that collected from a potential source of contamination, provides a less direct measure of particle character. The part of the source that would actually be inhalable upon dispersion should be separated from non-inhalable parts. If the mechanism of dispersion into air can be simulated, size-selective sampling can be used as described above. When a non-selective, total filter sample of airborne material is collected, the size distribution of the particles must be determined. Aerodynamic size classification by an instrument such as a cascade impactor gives the most accurate measure of size distribution. The deposition fractions in regions of the respiratory tract are determined from the measured size distribution. Analysis of dissolution of the particles collected on a total sample filter must taken into account potential confounding effects of particles that are not expected to deposit in the respiratory tract. Large particles contain a large mass of material, but present a relatively small surface area, resulting in relatively slow dissolution. Thus, a sample of a predominantly large particles (e.g., a 30- μm activity median aerodynamic diameter [AMAD] aerosol) would likely underestimate the dissolution rate of particles actually deposited in the lower respiratory tract.

When experimental dispersion of a source material is not practical, the particle size distribution in a bulk sample of the source material can be measured in the laboratory. Cases where only a small sample of particles can be collected, e.g., from a surface deposition associated with an inhalation exposure, usually require microscopic measurement of particle size. Particle shape, density, and specific activity must then be estimated to calculate the AMAD, making this the least accurate method of size analysis. These estimates are combined to approximate the activity-size distribution, to estimate regional lung deposition and to provide a qualitative evaluation of total particle surface area.

Guidelines are given to establish criteria for performing meaningful particle size and dissolution rate measurements for different types of samples. A decision scheme is presented for choosing the sample activity needed to obtain optimum results from dissolution measurements. Fractions of the simulated biological fluid are collected as the dissolution progresses on a schedule determined by the solubility and activity of the sample. A decision scheme to optimize the fraction collection schedule is also presented.

The retention class determined by dissolution rate measurement, together with the measured particle size distribution, give the information needed to apply the ICRP-30 model to assess inhalation exposures.

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GLOSSARY

a priori: done in advance to deduce an effect from a given cause.

a posteriori: done after the fact to induce a cause from an observed effect.

AED (aerodynamic equivalent diameter): the diameter of a unit-density sphere which has the same terminal settling velocity in air as the equivalent particle.

AMAD (activity median aerodynamic diameter): the AED of aerosol particles of median radioactivity content in a collection of particles which have been aerodynamically classified; calculation of the median usually assumes a log-normal distribution of particle size.

aerodynamic size classifier: a device which aerodynamically separates a stream of aerosol particles into two size fractions, one of which is usually deposited on a collection surface; this can be a series of separations as in the cascade impactor.

aerosol: a suspension comprised of particles larger than molecules, but small enough to remain airborne while carried by convective air currents.

cascade impactor: an aerodynamic size classifier which separates particles by impaction from a series of high-velocity jets; the cascade impactor is not in itself size-selective; it samples the total aerosol.

dissolution cell: a container of solvent in which a sample is dissolved over a period of time under controlled conditions.

dissolution rate: the rate at which the chemical compound of interest (measured by radioactivity) is dissolved while the solution is well below the point of saturation.

dissolution rate component: the mathematical component of a dissolution which is composed of more than one rate; these components are usually found to be exponential with time.

dynamic shape factor: the factor which relates the geometric diameter of a particle to its Stokes diameter; this, along with particle density, allows calculation of AED from geometric diameter (Hinds 1982).

GSD (geometric standard deviation): the factor which multiplies the median diameter to give one standard deviation of a log-normal distribution.

ICRP (International Commission on Radiological Protection): individuals from 20 countries organized to consider the fundamental principles upon which radiation protection measures can be based; reports and recommendations are published in Annals of the ICRP (Pergamon Press, New York).

immediate clearance: ciliary transport of particles from the N-P region and trachea to the esophagus, which takes place in a matter of minutes after deposition.

inhaled particles: aerosol particles that enter the respiratory tract during normal breathing, only some of which are deposited; there is no definition of size fraction associated with the term "inhaled particles."

inspirable fraction: aerosol particles of the fractional size distribution which deposit anywhere in the respiratory tract when inhaled; defined by ACGIH 1985, page 32.

interstitial lung fluid: the fluid which resides between the cells of the lung parenchyma; long-term retention of insoluble particles is in this chemical environment.

***in vitro*:** an artificial environment created for experimental purpose.

***in vivo*:** the living environment at the cellular level where normal life process is maintained.

log-normal distribution: a statistically normal distribution which has been geometrically skewed to the natural logarithm of the independent variable.

long-term dissolved fraction: the fraction of a sample which dissolves after the first day of dissolution; half-time of dissolution is the relevant measurement; may have a number of dissolution rate components.

macrophage: an independent, phagocytic cell found in large number in the lungs; active in the periphery of the lung, both on airway surfaces and interstitial spaces.

MMAD (mass median aerodynamic diameter): the AED of aerosol particles of median mass content in a collection of particles which have been aerodynamically classified; calculation of the median usually assumes a log-normal distribution of particle size.

nasopharyngeal region (N-P): airways of the nasal and pharyngeal cavities, including the larynx; ciliated epithelium immediately transports deposited particles into the esophagus.

PTFE (polytetrafluoroethylene): commonly called Teflon®; a remarkably inert substrate.

pulmonary deposition: the fraction of inhaled particles which deposit in the pulmonary region of the lungs at the time of inhalation; comprised of particles < 3.5 μm , 1.5 GSD median cut size by ACGIH definition of respirable fraction.

pulmonary region (P): airways peripheral to the terminal bronchioles; constitutes the vast majority of lung surface area and volume.

pulmonary retention: the fraction of deposited particles which are retained in the lungs for some period of time beyond the initial deposition of the particles.

readily dissolved fraction: the fraction of a sample which dissolves during the first day of dissolution; not represented by a half-time because it usually includes the transition to other components of dissolution rate.

respirable fraction: aerosol particles of the fractional size distribution which deposit in the pulmonary region of the lungs; defined by ACGIH as particles $\leq 3.5 \mu\text{m}$, 1.5 GSD median cut size.

respiratory tract: includes all airways from the anterior nares through the mouth and nasal cavities, the pharynx and larynx, the tracheobronchial tree, and the pair of lungs.

retention class: one of three classes of particle retention in the pulmonary region of the lung as defined in ICRP 30 (1979): D (days), W (weeks), and Y (years).

saturation value: the equilibrium concentration of a chemical in a solvent which contains a solid form of sample material as a source of the chemical of interest.

simulated gastric juice: a solution that represents the chemical environment of the stomach.

simulated lung fluid: a solution that represents the chemical environment of the pulmonary region of the lung; a surrogate interstitial lung fluid.

size-selective sampler: samples airborne particles according to their aerodynamic size; each size is collected with a definite efficiency, which can be chosen to correspond with pulmonary deposition.

solubility: the relative ability of a material to dissolve in a given solvent; limited by the saturation value.

specific surface area: the surface area of a material as a function of mass, which is determined by the surface-to-volume ratio; finely divided powders have a relatively high specific surface area on the order of m^2/g .

Stokes diameter: the diameter of a sphere which has the same density and terminal settling velocity as the particle with equivalent diameter.

thoracic fraction: aerosol particles of the fractional size distribution which deposit in the tracheobronchial and pulmonary regions of the lungs; defined by ACGIH as particles $< 10 \mu\text{m}$, 1.5 GSD median cut size.

tracheobronchial region (T-B): airways from the trachea out through the terminal bronchioles; these airways have ciliated epithelium.

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1.0 INTRODUCTION

Release of radioactive contaminants into the human environment can result in internal contamination by several routes: inhalation, ingestion, penetration through a wound, and absorption through intact skin. The most common mode of contamination is inhalation, which is also the most complex, involving all of the parameters of the other modes of contamination. Retention of material in the lung, fractions of inhaled activity that are taken up by the blood and body organs, and rates at which activity appears in the excreta are influenced by the rate at which the inhaled material dissolves to release transportable ions into the fluid medium of the lung. In the International Commission on Radiological Protection Publication 30 (ICRP 30) system of dosimetry (ICRP 1979), the lung retention and the amount and rate of uptake of a given material into the blood are evaluated by assigning the inhaled material to an empirical retention class. There are three recommended classes, in which materials are variously assumed to be cleared from the lung in the order of days (Class D), weeks (Class W), or years (Class Y). The ICRP recommends default classifications for some chemical forms of radionuclides. However, for the actinide materials of concern at the U.S. Department of Energy's Hanford Site, well-defined and simple chemical forms are rarely encountered in practice, and it is necessary to evaluate the likely clearance behavior of each of many diverse materials in order to make realistic assessments of doses. This need is accentuated in the case of decommissioning and cleanup operations, where prospective estimates of dose and risk are required for planning purposes. In cases of actual human contamination, biological monitoring can be used to refine the estimation of doses for the exposed individual.

The purpose of this report is to discuss experimental methods that can be applied to evaluate the rate at which materials containing actinides are likely to dissolve in biological fluids and to develop criteria to design meaningful measurement procedures. The discussion is focussed on the need to assign miscellaneous materials to one of the ICRP 30 retention classes for dose assessment purposes or, if necessary, to identify components of a given material that should be assigned to different classes. These procedures are oriented toward measurements needed for evaluation of airborne contamination.

Transport and deposition of particles depend on their aerodynamic size. Thus, procedures related to particle size-distribution measurements are also discussed.

The characterization of airborne particulates to model radiological dose to humans involves many variables. An investigation of a particular material might only have the ability to control or measure some of these variables. This document discusses criteria to identify the most important measurements that should be made and the criteria for good design of the experimental measuring system. Variance from the criteria presented in this document must be properly justified with consideration of all relevant parameters. In different situations, entirely different methods may be necessary to make the same kind of measurements. Many factors which vary from situation to situation must be considered to finalize a test method. This document aims to provide a basis for organizing the technical decisions that need to be made.

The following introductory sections outline the assumptions that underlie the ICRP 30 lung model and form the basis for the test criteria developed in this report. Chapter 2.0 discusses technical aspects of the measurement and interpretation of particle dissolution rates. For example, in cases where the nature of the material matrix is unknown, preliminary tests are needed to decide which method of dissolution measurement should be used. Procedures to measure dissolution of a very soluble material are generally different from those suitable for a relatively insoluble material. Chapter 3.0 discusses techniques that can be used to evaluate the likely size distribution of aerosols in exposure situations or to obtain a sample relevant to the assessment of an inhalation hazard. Chapter 4.0 develops criteria for splitting the available samples of materials into parts to assess both dissolution behavior and airborne particle size. Chapter 5.0 discusses the evaluation and interpretation of dissolution rate measurements, and their application to the ICRP 30 lung dosimetry model. Finally, Chapter 6.0 outlines the mechanistic approach to representing translocation of materials from the respiratory tract to the blood, an approach that is currently being proposed to ICRP Committee II by the Task Group to Review the Lung Model. If adopted by the ICRP, this approach will explicitly utilize any reliable experimental data on the rate at which materials dissolve in biological fluids, in a new model of dose to respiratory tissues and translocation to body organs and excreta. Two

appendixes to this report present schematic decision trees to guide the selection of sample activity needed to carry out dissolution measurements, and the design of measurement schedules, for diverse materials as a function of their dissolution rate.

1.1 INHALATION EXPOSURE TO RADIOACTIVE CONTAMINANTS

Physical dispersion of a material may cause a substantial amount of contaminant to form aerosol particles, which may be small enough to remain airborne for many minutes and be carried long distances by convective air currents. The physical nature of the matrix of the material, as well as the mechanism of dispersion, will determine the size distribution of the particles dispersed into the air. The aerodynamic size of the particles influences the likelihood that they will be inhaled and also the fraction and site of their deposition within the respiratory tract. Particles larger than about 10- μm AED^(a) are less likely to be inhaled than smaller particles (see Figure 1.1). Inhalation exposure to smaller particles is strongly influenced by air motion and the geometry of the environment. The most reliable measurements of intake are those obtained from personal air sampling (ACGIH 1983). Ideally, samples of particles used to assess the hazard posed by a given intake should have the same size distribution as those that would be inhaled and deposited in the respiratory tract. Size-selective samplers are available to simulate the particle-size discrimination characteristics of the respiratory tract (ACGIH 1985).

To assess the potential hazard in a given situation, physically simulating the most likely dispersion process and sampling the resulting airborne particles would be the most effective way to model the potential human exposure. This would constitute an *a priori* assessment of the potential hazard. When a sample is collected after an actual exposure incident to characterize the exposure, this is referred to below as *a posteriori* assessment.

(a) Particle diameter throughout this document is the aerodynamic equivalent diameter (AED) for particles > 0.5 μm . Smaller particles are best referred to their volume equivalent diameter. In either case, radioactivity is the quantitative measure for distribution of particle size.

FIGURE 1.1. Efficiency of Inhaling Dust Particles Measured by Various Authors Under Moving or Still Air Conditions

The majority of the mass and radionuclide activity in a bulk source material is often associated with large particles. The respirable particles could be qualitatively different than the average character of the bulk material from which they were dispersed. Thus, it is important to consider the source in terms of the material that would actually be dispersed in the inhalable or respirable size range.

Inhaled particles are deposited throughout the respiratory tract. The regional distribution of these particles depends on many variables. Most important is the physical size of the particles (ACGIH 1985). A release caused by some uncontrolled mechanical process would likely involve a wide range of particle size. The activity median aerodynamic diameter (AMAD) of an inhaled aerosol is the parameter that determines the fraction of the intake that is deposited in each region of the respiratory tract (ICRP 1979). The total amount of activity transported to the blood and its rate of transfer are then influenced by the fractionation of the intake between the nasopharynx (the N-P region), the tracheobronchial region (T-B), and the pulmonary region (P), as well as by the retention class to which the material is assigned in

the ICRP 30 model. Relatively large particles ($20\text{ }\mu\text{m}$ and larger) are assumed to be deposited quantitatively in the upper respiratory tract (represented in the ICRP 30 model by the N-P region), from which they can be cleared and swallowed to enter the gastrointestinal (GI) tract. In this case, to assess the amount of systemic intake, it is important to know the solubility and dissolution rate of the material in the acid environment of the stomach.

Inhaled fine particles ($0.1\text{ }\mu\text{m}$ to $2.5\text{ }\mu\text{m}$) are deposited predominantly in the lower respiratory tract (the bronchial tree and lungs); thus, it is important to know the solubility and dissolution rate of these particles in the lung. Intermediate size particles ($2.5\text{ }\mu\text{m}$ to $15\text{ }\mu\text{m}$) are deposited in both the upper and lower respiratory tract. Ultrafine particles ($< 0.1\text{ }\mu\text{m}$) are also deposited in both the upper and lower respiratory tract. To predict the long-term pulmonary retention and the amount of systemic uptake of relatively insoluble contaminants, it is thus useful to evaluate the dissolution rate of particles less than $15\text{ }\mu\text{m}$ in environments that simulate the lungs. Criteria for measurement of particle dissolution in both simulated lung fluid and gastric juice are summarized in Section 2.2. Criteria for measurement of the particle size distribution of samples of material are summarized in Section 3.2.

1.2 CLEARANCE AND RETENTION OF INHALED CONTAMINANTS

Measurements of particle size and dissolution rate provide input to the ICRP 30 model to assess the dosimetric consequences of exposure to airborne contaminants. There are basically two parameters involved: the region of deposition in the respiratory tract, which is primarily determined by the aerodynamic size of the particles, and fraction and rate at which the radionuclide is absorbed into the blood from each region. Estimates of the aerosol size distribution and retention class are used in the ICRP model to predict the clearance, translocation, and retention of the inhaled contaminant. In actual exposure cases, the amount of activity excreted may be measured to refine the initial estimates of retention class or aerosol size.

The ICRP 30 model (ICRP 1979) is shown in Figure 1.2. The respiratory tract is divided into three distinct regions: N-P, T-B, and P regions. Extrathoracic airways (also called the upper respiratory tract) include the nasal passages, mouth, pharynx, and larynx, and are referred to as the N-P

FIGURE 1.2. ICRP 30 Mathematical Model Used to Describe Clearance from the Respiratory System. Various clearance pathways from Compartments a-i are shown in the four respiratory regions, N-P, T-B, P, and L.

TABLE 1.1. Application of Current ICRP 30 Model for Aerosol of 1- μ m AMAD

Region	Compartment	Class					
		D		W		Y	
		T day	F	T day	F	T day	F
N-P ($D_{N-P} = 0.30$)	a	0.01	0.5	0.01	0.1	0.01	0.01
	b	0.01	0.5	0.40	0.9	0.40	0.99
T-B ($D_{T-B} = 0.08$)	c	0.01	0.95	0.01	0.5	0.01	0.01
	d	0.2	0.05	0.2	0.5	0.2	0.99
P ($D_P = 0.25$)	e	0.5	0.8	50	0.15	500	0.05
	f	n.a.	n.a.	1.0	0.4	1.0	0.4
	g	n.a.	n.a.	50	0.4	500	0.4
	h	0.5	0.2	50	0.05	500	0.15
L	i	0.5	1.0	50	1.0	1000	0.9
	j	n.a.	n.a.	n.a.	n.a.	∞	0.1

Source: ICRP 30 (1979, p. 25). The values for the removal half-times, T_a to T_j and compartmental fractions, F_a to F_j are given for each of the three classes of retained materials. The values given for D_{N-P} , D_{T-B} and D_P (left column) are the regional depositions for an aerosol with an AMAD of 1 μ m. n.a. = not applicable.

region. The trachea, bronchi, and ciliated bronchioles comprise the T-B region. The remainder of the lungs, including respiratory airways and pulmonary parenchyma, is referred to as the P region. Fractional deposition of inhaled aerosol in these three regions is represented by the parameters D_{N-P} , D_{T-B} , and D_P . Aerodynamic size of the particles (or thermodynamic size for particles smaller than $0.5 \mu\text{m}$) is the primary determinant of regional deposition. The example given in Table 1.1 is for an aerosol of $1\text{-}\mu\text{m}$ activity median aerodynamic diameter (AMAD) with a typical geometric standard deviation (GSD) or dispersion in particle size. The model assumes that 30% of the intake is deposited in the N-P region, 8% in the T-B region, and 25% in the P region; the remaining 37% is exhaled. Deposition fractions for other median particle sizes are given in ICRP 30 (ICRP 1979, p. 24).

The regions of the respiratory tract have different characteristics for clearance of deposited particles. Each region is divided into compartments, with some fraction (F) of the deposited particles assigned to each compartment in that region. Compartments a, c, and e involve the direct absorption of material into the body fluids, which is strongly influenced by the dissolution rate of the material. Compartments b, d, f, and g are associated with physical transport processes, including mucociliary transport through the T-B region to the GI tract. The pulmonary lymphatic system (L) retains particles transferred from the P region. ICRP 30 treats L as a separate region of the respiratory tract for clearance purposes, but not for dosimetry, where radioactive decays in the T-B, P, and L regions are assumed to contribute equally to the dose received by the composite 1-kg mass of "lung" tissue. The rates of clearance for all the compartments are formulated as first-order differential equations in ICRP 30 (ICRP 1979).

The overall effective rate of clearance, which determines retention, is a combination of absorption rates and mechanical clearance rates of the compartments (represented by half-times T). Partition of activity between the two pathways is affected by the dissolution rate of the material. Thus, particles with large dissolution rate half-times involve considerable mechanical clearance, whereas materials with small half-times mainly involve absorptive clearance. ICRP 30 divides materials into three retention classes: "D" for half-times less than 10 days, "W" for half-times from 10 to 100 days, and "Y" with half-times greater than 100 days. Some chemical forms of radionuclides

are given assignment to retention classes by the ICRP 30 Metabolic Data sections. Often, however, these assignments do not include the material of interest, or may not consider an important aspect such as crystalline form of the material. Retention class of the material must be assigned based on the best available information, which may be supplemented to the present model (ICRP 30 1979-1982).

Measured rates of dissolution in simulated biological fluids can be used to assign a material to an ICRP 30 retention class. If the material has just one principle component, the half-time of dissolution can be used to assign it to one of the three available classes. In a case where there is more than one component to the dissolution rate, each component can be separately assigned to the most appropriate available retention class. If the material has more than one component of dissolution and it is desired to place the material into a single retention class, the weighted average dissolution rate may be used as described in Chapter 5.0. The best basis for retention class assignment is *in vivo* data, which should be given precedence owing to the attenuation of transport by tissue binding of the material. Without this biological information for the exact chemical form of the material, retention class assignment is based on measured dissolution rate in simulated biological fluids. *In vitro* dissolution has been found to correlate with *in vivo* transportability from the respiratory tract by several investigators (Kanapilly et al. 1973, Morrow et al. 1968).

A fraction f_1 of the material that enters the GI tract, either by ingestion or by clearance from the respiratory tract, is absorbed from the GI tract into the body fluids. The chemical environment in the stomach is considerably different from that in the lungs. Hence, the classification of a material for transportability from the lung is not directly applicable to the determination of f_1 . As with the lung retention classification, values of f_1 are assigned for some chemical forms of radionuclides by ICRP 30 in the Metabolic Data sections of that report. However, if the recommended values of f_1 can be shown to be inappropriate for the material of interest, ICRP 30 recommends further that a more specific value should be substituted: "Values of f_1 listed may not always be applicable in practice and the user should make his own choice from the values given, interpolating between values where appropriate" (ICRP 1979, p. 52). The dissolution rate of a material in

simulated gastric juice can provide a basis for an estimate of f_1 . This estimate, however, must be related to the same type of dissolution measurement of a reference material for which the value of f_1 is well established. Hence, there is a need to establish a data base for dissolution of a variety of materials in standard simulated body fluids, which would allow cross-referencing to existing measurements of metabolic behavior.

2.0 MEASUREMENT OF DISSOLUTION IN SIMULATED BIOLOGICAL FLUIDS

There are two body fluids of primary interest: lung fluid and gastric juice. Ingested or swallowed material will be exposed to the acid environment of the stomach for approximately 1 hour. The solubility of materials in gastric juice, which is essentially 0.1-M HCl, is often very different from the solubility in lung fluid. For the inorganic materials of interest, dissolution is generally faster in HCl. Miglio, Muggenburg, and Brooks (1977) demonstrated that in addition to providing information relative to dissolution in the GI tract, dissolution in HCl gives a fast method of estimating dissolution of the material in the lungs. They also demonstrated that dissolution in HCl is fairly insensitive to temperature and other variables. Hence, dissolution in simulated gastric juice is a relatively quick and reproducible method to establish the length of time needed for measurement of dissolution rate in simulated lung fluid. However, the relationship between dissolution in simulated gastric juice and in simulated lung fluid must be established for each material of interest.

Insoluble particles deposited deep in the lungs are subject to two different environments: interstitial lung fluid and that within macrophages. Particles in macrophage lysosomes are subjected to a fairly acid solution; Nilsen, Nyberg, and Camner (1988) found the pH to be about 5 within phagolysosomes. However, long-term retention in the lungs is believed to be mainly in the interstitial lung fluid environment, with some retention within macrophages which reside in the interstitial space; the ratio of the two compartments has not been established. Dissolution within macrophages has been measured *in vitro* (Kreyling et al. 1986; Lirsac, Nolibe, and Metnier 1989; Marafante et al. 1987). Future investigations may include *in vitro* measurement in macrophages. However, this is not yet established as a method for dissolution measurement and will not be further referenced in this document.

A simulant of the interstitial lung fluid has been described by Moss (1979), the formula of which is given in Table 2.1. This formula has been used by several other investigators and can be considered the standard simulated lung fluid (SLF) formula. A variation of this formula is the addition of a chelating agent such as DTPA (diethylenetriaminepentaacetic acid, 0.079 g/L) in order to avoid polymerization or precipitation of the

TABLE 2.1. Chemical Formula for Simulated Lung Fluid

<u>Lung Fluid Chemical Components</u>		<u>g/L</u>
Magnesium Chloride	$\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$	0.203
Sodium Chloride	NaCl	6.019
Potassium Chloride	KCl	0.298
Sodium Phosphate	$\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$	0.268
Sodium Sulfate	Na_2SO_4	0.071
Calcium Chloride	$\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$	0.368
Sodium Acetate	$\text{NaH}_3\text{C}_2\text{O}_2 \cdot 3\text{H}_2\text{O}$	0.952
Sodium Bicarbonate	NaHCO_3	2.604
Sodium Citrate	$\text{Na}_3\text{H}_5\text{C}_6\text{O}_7 \cdot 2\text{H}_2\text{O}$	0.097

radionuclides. The presence of DTPA, however, may alter the dissolution rate; therefore, DTPA is not included in the formula. The goal of dissolution rate measurement is to simulate the dissolution of the particles in the pulmonary region of the lungs.

There is no well-established procedure for the measurement of dissolution of a sample material. A goal of this document is to set the criteria on which such a procedure can be based. The methods of Kalkwarf (1983) have been referenced by other investigators of dissolution rate measurement; these methods meet some of the criteria developed below. The criteria are generally applicable to dissolution in both simulated gastric juice and simulated lung fluid.

2.1 CRITERIA FOR DISSOLUTION RATE MEASUREMENTS

The following guidelines should be used in establishing criteria for measurement of dissolution of a sample material.

2.1.1 Sample Collection and Handling

A goal is to collect a sample that accurately represents the particles which would be deposited in the respiratory tract, both in terms of quality and quantity. The best sample would be collected in the breathing zone of any worker or other person who may be exposed. Collection may have to be made at less representative sites, where the method of collection must consider the potential mechanism of dispersion. The sampling device should collect only

the respirable (or inspirable) fraction of aerosol particles on a filter by using a technique for aerodynamic size classification. There is no established method for measurement of the dissolution of particles that have been collected by impaction onto a solid substrate. Thus, a classifier such as a cyclone is more suitable for collection of the total respirable fraction of an aerosol onto a filter. Size-selective sampling of aerosols has been extensively addressed by ACGIH (1985). Measurement of the chemical quality of the respirable (inspirable) particles is the primary goal of the dissolution measurement.

The medium on which the sample is collected should be chemically inert. A polytetrafluoroethylene (PTFE, commonly called Teflon®) filter medium should be used. Glass fiber filters must be avoided for sampling of particles because glass surfaces are known to bind some actinide compounds. If loose dust is to be collected from a surface without aerodynamic particle size classification, then it should be collected by suction onto a PTFE filter. Other samples which cannot be collected on a PTFE filter, such as pieces of fabric or swabs, should be processed by the centrifuge method of dissolution measurement, as described below.

The medium on which the particles are collected should be of minimal size. Any excess bulk should be cut away from the sample. For example, the tip of a swab should be cut off and the handle discarded. A dry sample should be placed in a metal container (for protection from electrostatic fields) which may then be sealed in a plastic bag. Storage of filter samples before dissolution measurement should be in the holder that was used to collect the sample of particles. This should be stored in a dry metal container. Wet samples must be placed in small plastic vials and tightly sealed. Wet samples should not be stored for any length of time; these should be processed as soon as possible. The time between collection of the wet sample and start of the dissolution measurement must be considered as part of the period for the "rapidly dissolved fraction," which appears with the first dissolution fraction. If the first fraction is collected at 1 hour, then the pre-dissolved

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activity will be present in this fraction. The elapsed time and storage conditions between sample collection and dissolution measurement should be recorded.

The amount of activity in a sample must be estimated. If there is some control of the amount of activity collected in a sample, it should be chosen according to the expected solubility. The relationship of dissolution rate and solution saturation value (solubility) is not known. Samples of highly soluble compounds should have less mass in order to avoid saturation of the dissolution fluid (or a larger dissolution cell could be used to lower the sample mass to solution volume ratio). If the material is believed to dissolve rapidly ($T_{1/2} < 1$ day), the amount of mass must be low enough to result in a chemical solution $< 10\%$ of the saturation value with a given fraction collection schedule. As solution concentration approaches the saturation value, the rate of dissolution decreases. When the concentration is kept below 10% of the saturation value, the rate of dissolution is relatively insensitive to changes in concentration. Relatively insoluble materials ($T_{1/2} > 100$ days) should have more mass in order to achieve detectable quantities of activity in the dissolution fluid, which may require a dissolution fraction sampling schedule that has a minimal number of fractions. Different methods of radioactivity analysis may be needed to achieve an adequate limit of detection. The available choices of the radioactivity analysis method should be included in the dissolution measurement procedure. Considering the many variables involved, a decision chart should be made for choosing the size of the sample. An example of such a chart is given in Appendix A.

A material of unknown dissolution characteristics should be submitted to a preliminary dissolution test in simulated gastric juice in order to decide the appropriate sample size needed and the proper schedule of dissolution measurement samples.

2.1.2 Specifications of the Dissolution Measurement Procedure

The procedure should use the simulated lung fluid described by Moss (1979, see Table 2.1). If a sufficient quantity of the sample is available, the dissolution should first be measured in simulated gastric juice (1.19 g/L KCl in 0.145 mole/L HCl). During dissolution, the solution must be constantly

shaken or stirred, and maintained at 37°C to simulate physiological conditions. The pH of the simulated lung fluid should be maintained between 7.2 and 7.6 by bubbling CO₂ through the solution. A sealed dissolution cell should remain at a constant pH value. All parts in contact with the simulated lung fluid should be PTFE; no glass or metal should come into contact with the dissolution fluid for any greater time than is necessary to carry out the measurement procedure in order to minimize chemical reaction with surfaces. Some forms of transuranic compounds have been found to bind to glass surfaces, which required etching with hydrofluoric acid to put the compounds back into solution. Any plastics other than PTFE are preferable to metal or glass.

All parts in contact with the simulated lung fluid should be sterilized before use (bacterial growth in simulated lung fluid can be a problem). Dissolution fluid handling and sampling must carefully maintain sterility of the dissolution cell, which will require some procedures in addition to radio-nuclide contamination control. So-called laminar flow biological safety cabinets are best for the combination of radiochemical containment and biological control. The dissolution cell would be opened only within the cabinet. If a biological safety cabinet is not available, the dissolution cell should only be opened briefly for transfers using equipment which is sterilized immediately before use. Sterilization of the sample itself is also important. This must be done in a way that does not alter the physical or chemical nature of the particles. For many dry samples, this could be accomplished with heat or ethanol vapor. Wet samples might require γ -irradiation or ethylene oxide.

Two methods for measurement of dissolution rate are acceptable: the "sandwich" method and the centrifuge method. For the sandwich method, the filter is transferred from the contaminated collection holder to a clean sterile plastic open-face filter holder. Particles that have been collected on 25-mm PTFE filters are processed directly by sealing a 0.1- μ m Nuclepore® filter over the collection surface. This "sandwich" is placed directly into the dissolution fluid; no attempt is made to remove the particles from the sample filter. The PTFE dissolution cell container should be of a size just large enough to accommodate the filter holder. Dissolution fluid may be

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withdrawn from the cell without disturbing the sample. However, the sample must not be allowed to become dry during the change of dissolution fluid. The filter must also be maintained in a horizontal position with the Nuclepore barrier filter on top. At the end of the dissolution, the filter sandwich is removed from the holder and assayed for the remaining activity.

Most samples, other than those collected on filters, require the centrifuge method. In this method, the dissolution cell can be centrifuged at $10,000 \times g$ for 10 minutes before withdrawing an aliquot of the supernatant, which is replaced with the same volume of sterile dissolution fluid. The supernatant is not to be decanted, nor is the pellet to be disturbed. This can be accomplished by carefully pipetting as much as 90% of the supernatant. For samples processed with this centrifuge method, the dissolution cell should be a PTFE centrifuge tube. Activity in the dissolution fluid which remains from the aliquot removal must be accounted for in the calculation of dissolution half-time. At the end of the dissolution, the remaining sample is assayed for activity, again accounting for the dissolution fluid left with the sample.

2.1.3 Information to be Obtained to Apply the ICRP 30 Lung Model

The goal is to provide dissolution half-times for each rate component of the sample. If the material is of high solubility, it may dissolve so rapidly that no long-term dissolution fraction will be measurable. If the material is of low solubility and homogeneous, there will likely be a "readily dissolved fraction" (that which dissolves in the first day) to complement the "long-term dissolved fraction" (which dissolves after the first day). Molecules loosely bound to the surface of particles rapidly dissolve into the solution. The relative size of these two fractions depends on the surface properties of the material, which is strongly influenced by the specific surface area of the sample (Mewhinney et al. 1987). A typical sample of material may have a mixture of material components of different solubility, which will give a number of components to the rate of dissolution.

The dissolution cell sampling schedule must be adjustable to provide as many data points as practicable for a given rate component of the dissolution. The basic sampling schedule should include at least hour 1, day 1, day 10, and day 100. This would be adjusted for rapidly dissolved samples, very insoluble

samples, or low activity samples. Examples are given in Table 2.2. These three classes of dissolution approximately correspond to the three classes of transportability in the ICRP 30 lung model. An example of a decision scheme to determine the fraction collection schedule is given in Appendix B. The sampling schedule should be reconsidered as each sample is analyzed for activity.

If the collected fraction approaches 10% of the estimated chemical saturation value, fractions need to be collected more often. If the saturation value is not known, it must be determined from a separate sample. A sample similar to that processed with the dissolution measurement procedure could follow the same procedure except that only small aliquots would be withdrawn and no solvent would be added to replace the aliquot volume. The concentration of the solution should then approach saturation value. In some cases, where dissolution is very slow, it may be desirable to make a retrospective evaluation of solution saturation. Concentration of the solute would be determined for each fraction and later compared to the saturation value.

The total amount of activity dissolved should be at least 95% of the sample for relatively soluble materials. For relatively insoluble materials, with a substantial component of greater than 30-day half-time, the fraction of dissolution may not reach this value in a reasonable length of time. Then, dissolution should be conducted for the longest practical length of time, which will give a minimum value of dissolution rate to the longest-term component of the dissolution. A detailed procedure for adjusting the sampling schedule (similar to Appendix B) should be included in the measurement

TABLE 2.2. Examples of Dissolution Fraction Collection Schedules

<u>Rapid Dissolution</u>		<u>Medium Dissolution</u>		<u>Slow Dissolution</u>	
hour	1	hour	1	hour	1
hour	4	day	1	day	1
day	1		4		10
	2		10		100
	10		30		200
	100		100		300

protocol. Materials that are a combination of relatively soluble and insoluble materials require consideration of both possible saturation at early times and minimum detectable quantities at later times. The minimum fraction of long-term dissolution rate component must be decided in advance, and the sampling schedule set up to accommodate the ratio of relatively soluble to insoluble fractions. This might require more frequent samples during the first few days of dissolution, and less frequent samples during the later months of dissolution.

Simulated lung fluid is not a very stable mixture; thus, measurements of dissolution rates in simulated lung fluid beyond 300 days would be questionable because of the uncertainties involved. Such samples would probably not add much reliable information to the estimation of the long-term dissolution half-time, except in the case of extremely insoluble material. The point of diminishing return on the investment of effort will have to be decided for each sample. Owing to its chemical stability, dissolution in simulated gastric juice would be a more reliable measurement for long-term components of the dissolution, which could be used as an estimator of long-term dissolution in simulated lung fluid. The relationship of the dissolution in the two fluids needs to be established for the material before any extrapolation can be made. A valuable result of dissolution in simulated gastric juice is the measure of the ratio of relatively soluble and insoluble fractions in the sample material. Estimates of long-term dissolution should include a statistical analysis which provides limits on upper and lower bounds on the half-time of dissolution.

2.1.4 Acceptance and Interpretation of Results

Violation of any established criteria will disqualify a sample for acceptance of the dissolution measurement. These criteria are to be specified in the measurement protocol and must be checked off by the person conducting the dissolution measurement for each sample. For example, if a dissolution fraction is found to have in excess of 10% of the saturation value, the measure of dissolution rate is not acceptable.

Some conditions of sample collection and analysis will influence the interpretation of measurements. The dissolution measurement procedure will specify the factors to be reported with the results of measurement for each

sample. The report should include a detailed description of sample collection, which includes an accurate drawing of the site of particle release and a description of the mechanism of dispersion. Use of these measurements for assessment of biological hazard is discussed in Chapter 5.0.

2.2 SUMMARY OF CRITERIA FOR DISSOLUTION RATE MEASUREMENT

The main points of criteria for dissolution rate measurement are summarized below.

- Use PTFE filter media for sample collection where possible; avoid glass fiber filters or other reactive materials.
- Use minimal surface area of collection media, especially when materials other than PTFE filters are used.
- Process wet samples immediately; dry samples should remain dry until the dissolution process.
- Estimate total activity initially in the sample to adjust the schedule for dissolution fraction collection appropriately.
- Use simulated lung fluid for dissolution, and if a second sample is available, then also use simulated gastric juice.
- Constantly shake or stir dissolution cells and maintain them at 37°C.
- Use sterile PTFE for all parts of the dissolution cell that come into contact with the dissolution fluid; otherwise, minimize contact with other materials.
- Carry out a preliminary test in simulated gastric juice when the general solubility characteristic of the material is unknown.
- Measure half-times of all discernable rate components of dissolution, accounting for at least 95% of sample activity.
- Measure dissolution fraction at 1 hour, 1 day, 10 days, and 100 days in all cases, and at other times depending on sample solubility and activity.
- Ensure that collected fractions of dissolution fluid are free of particles greater than 0.1 μm in diameter.
- Ensure that collected fractions of the dissolution fluid have concentrations less than 10% of the saturation value.
- Establish acceptance criteria for each investigation; these should include the criteria listed above.

- Record that all established criteria have been fulfilled for each investigation.

3.0 MEASUREMENT OF PARTICLE SIZE DISTRIBUTION

Samples that accurately represent the particle size distribution of an inhalation exposure are difficult to obtain. In the work environment, it is generally not practical to continuously monitor the size of airborne particles. Instrumentation is not currently available for continuous monitoring of airborne particle size as a function of radioactivity. This means that grab samples must suffice to provide aerodynamic particle size classification at the time of release. Cascade impactors are the most commonly used instruments for aerodynamic size measurement of radioactive particles (AIHA 1986). In the event of an accidental exposure, grab samples would not usually be available. An alarm system might be used to trigger grab samplers, but this would require elaborate control. When aerodynamic methods are not available, a collected sample may be analyzed, as described below. Thus, aerodynamic particle size classification is generally suited only to experimental simulation of a release for *a priori* samples, i.e., samples collected from an experiment which is expected to reproduce the airborne dispersion of particles that would result from an inadvertent release.

The choice of a suitable method of particle collection for size measurement must consider all of the procedures, factors, and limitations involved. Complete measurement of the airborne particle size distribution with a cascade impactor gives the most information. Aerodynamic size classification does not involve measurement of individual particles; they are collected according to size while they are airborne, which is an analog process. Size-selective sampling by aerodynamic size classification into respirable (or thoracic or inspirable) fraction gives less information, but is relatively simple and is a realistic measure of exposure in relation to potential lung deposition. The fraction of particles of a given size, collected by a size-selective sampler, represents the fraction that would deposit in the lungs when inhaled. The ICRP definition of pulmonary deposition corresponds to the ACGIH definition of respirable fraction of the aerosol. Size-selective samplers, which collect a sized fraction onto a filter, have the advantage that they can be operated for relatively long periods of time without becoming overloaded. The measured activity on the filter can be compared to the activity collected on a total sample filter for

a quantitative value of the respirable fraction of the aerosol. The filter (preferably PTFE) with the respirable fraction also serves as the best sample for measurement of dissolution in simulated lung fluid.

Air-sampling cyclones are commonly used to collect the respirable particle fraction ($< 3.5\text{-}\mu\text{m}$ median cut diameter with 1.5 GSD) onto a filter (ACGIH 1983). Additional size cuts such as the thoracic particle fraction (median cut diameter $10\text{ }\mu\text{m}$, 1.5 GSD) can be made with additional size-selective devices; however, for long-term retention of insoluble particles, the respirable fraction is the most relevant. The aerodynamic cut diameter selected by the cyclone depends on the flow rate through the cyclone. Particles that are drawn into the sampler but not selected are collected in the large-particle collection cup of the cyclone. These particles partially represent the inspirable fraction. However, the size-cut of the cyclone inlet is not well characterized, so size information is only approximate. The large particles collected in the cup should be used as the sample to measure dissolution in simulated gastric juice, since these represent particles that would deposit in the upper airways and be cleared to the stomach.

A continuous sampler such as an open-faced filter will generally be stopped for collection of the sample medium soon after a major release. This does not provide aerodynamic particle-size classification; the particles must be sized after collection. The first assumption is that all of the activity in the sample is from the event of interest. Then, particles in a representative portion of the sample are to be sized. Reconstruction of the airborne particle size distribution from a collected sample of particles involves many types of measurements or assumptions in addition to the geometric dimensions of the particles (Hinds 1982). Many different methods are available for this *a posteriori* sample analysis of particle size (Herdan 1960), i.e., samples that were collected after the fact and used to estimate the conditions at the time of accidental release. Choice of a method depends on the analytical instrumentation available.

Choice of a particle size measurement method must meet the criteria given below, which are different for each of three modes of particle collection:

- A) aerodynamic size classification

B) bulk sample of the particle source

C) sample collected on the surface of some medium, such as a filter, horizontal surface, or smear of a deposition surface.

Important criteria for each of these three modes of collection are given in the following sections of this chapter.

The relationship of particle size to dissolution rate of a reasonably homogeneous material is primarily determined by the specific surface area (Mercer 1967). Measurement of specific surface by the BET method (Brunauer, Emmett, and Teller 1938) would require at least 10 mg of representative powder to be available. Knowledge of the specific surface area of the material would allow the extrapolation of dissolution rate from a sample of one particle size distribution to another size distribution. This would be useful information for modelling of inhalation exposure health risk, but is not necessary for measurement of dissolution or particle size distribution.

3.1 CRITERIA FOR PARTICLE SIZE MEASUREMENT

The following guidelines should be used in establishing criteria for measurement of particle sizes.

3.1.1 Sample Collection and Handling

The collected sample must be representative of the actual exposure to be evaluated. Sampling of airborne particles is a substantial discipline in itself (ACGIH 1983). It is the subject of specialized industrial hygiene and should have its own criteria for each type of material. The amount of activity sampled depends on the mode of collection and the method for analysis. In all cases, the amount of sample is relatively small; accurate representation of the size distribution is the most important factor. The following paragraphs discuss sample collection and handling for each of the three modes of particle collection:

A) Aerodynamic size classification. Aerodynamic collection with a total sampling instrument such as a cascade impactor is limited by the mass collected on any one stage. The upper bound is approximately 100 μg per jet in the stage, and the minimum detectable activity on a stage serves as the lower bound. An estimate of the aerosol mass concentration must be made, and the length of sampling time calculated from the mass loading limit of the instrument. A size-selective sampler, such as the 10-mm cyclone, is limited by flow restriction of the collection filter by the mass load; if the

aerosol is of a dry material, then the filter should accommodate several milligrams, which should be more than adequate for dissolution measurement.

- B) Bulk sample of particle source. If a sample of the bulk source material is aerosolized, then it is treated as with mode A. In an alternative method, measurement of the Stokes diameter in a liquid requires a quantity of the powder within a range specified by the manufacturer of the sedimentation cell. If a dynamic method is not used, then geometric size and shape of the particles must be measured. The method of geometric size analysis requires a small representative portion of the bulk powder which amounts to the desired number of particles for analysis. At least 1000 particles should be measured; the practical upper limit will depend on the method. The method of suction onto a filter might be the most practical. This would tend to bias the sample toward smaller particles which are also more representative of airborne dispersal. The size of the inlet tube should be chosen to act as a vertical elutriator (Mercer 1973, p. 297). Samples for direct electron microscopy should collect a number of particles, which produces good separation on the surface. Of course, constraints associated with collection and handling of radioactive materials must be accommodated. These constraints may be especially important when working with bulk source material.
- C) Surface collection of sample. When the collected particles must be removed from the surface of collection, the medium of collection must be amenable to the process of particle removal. If the particles were collected by gentle settling on the surface, then they should be fairly easy to remove. These particles are then subject to the criteria for geometric measurement for mode B. If the particles were deeply embedded in the surface, then it may be difficult to extract a representative portion. Particles collected on most types of filter are embedded to some depth according to particle size. Smaller particles are typically deposited deeper in the filter, where they are difficult to remove. Any attempt to remove particles from the filter would be strongly biased toward the larger particles. The only type of filter suited to efficient particle removal is the Nuclepore filter, which is also well suited to direct electron microscopy. For particle size analysis, it is best to avoid any particle removal or transfer process which might bias the size distribution. Thus, direct electron microscopy should be used whenever possible.

Storage of the sample before particle size measurement must keep the particles dry, unless they were originally collected in a wet form and are to be processed by a wet method. The main object is to prevent the particles from experiencing the transition between wet and dry conditions (Mewhinney, Eidson, and Wong 1987). Samples collected under wet conditions would not likely be representative of an inhalation exposure, unless the deposition

mechanisms simulate those in the respiratory tract. A detailed account of the collection and handling procedure must always be reported.

3.1.2 Specifications of Particle Size Measurement Procedures

The following paragraphs discuss particle size measurement procedures for each of the three modes of particle collection:

- A) Aerodynamic size classification. For aerodynamic particle size classification, the size measurement is accomplished in the instrument (ACGIH 1983). The remaining measurement is of the activity in each size class or stage of the instrument. A suitable detector must be chosen for the radiation of interest.
- B) Bulk sample of particle source. Aerosolization of the bulk powder must be done with a method specifically designed to simulate the dispersion of the powder during an actual release. Measurement of the airborne particle size is then subject to the same criteria as collection mode A. Measurement of the Stokes diameter by sedimentation in a liquid must follow the procedure of the instrument manufacturer (e.g. Micromeritics SediGraph 5000®). A high-vacuum electrobalance can be used for the density measurement. The Stokes diameter and the particle density can be used to calculate the AED and MMAD. The distribution of specific activity by particle size must be known to calculate the AMAD. Geometric measurement of particle size will depend on the equipment used for the measurement. A characteristic diameter, which gives the most information about shape of the particles, should be measured (Herdan 1960).
- C) Surface collection of samples. An effective method of particle removal must be devised for each medium of particle collection. It should be demonstrated that at least 90% of the activity is removed from the medium, in order to be sure of a representative sample. If only a small fraction of the particles is removed, then it might be strongly biased toward some particle size. This is typically a problem with particles collected on a filter, as described in the previous section. Once the particles are in suspension, then geometric measurement is made, as with samples collected by mode B.

When the geometric sizes of particles are measured by an optical method, knowledge of the heterogeneity of the material is needed. In some cases, the sample would be a mixture of radioactive and nonradioactive particles which may be of different size distributions. If enough material has been collected, then the specific activity of at least three size fractions should

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be measured. For a relatively insoluble material, the size fractionation can be accomplished by sedimentation in a liquid. Each fraction would then be dried, weighed, and counted for specific activity. Small samples which do not allow fractionation can be tested for heterogeneity by electron microscopy of autoradiographs. With appropriate exposure of the applied radiographic film, geometric size of the particles can be measured along with a count of the associated α tracks.

3.1.3 Information to be Obtained to Apply the ICRP 30 Lung Model

Particle size is of use only if it is known to be representative of the potential exposure. The ICRP 30 lung model includes the aerosol AMAD in the evaluation of doses from inhalation exposure. Use of this information in the ICRP 30 model is described in Chapter 5.0. The following paragraphs discuss application of the results obtained from each of the three modes of particle collection:

- A) Aerodynamic size classification. Aerodynamic particle size measurement can be used directly in the ICRP 30 model. If the aerosol has log-normal size distribution, then the AMAD is reported, along with GSD and a test of statistical significance of log-normality. Otherwise, the size class measurements are reported with an estimation of the fractions in the respirable ($< 3.5 \mu\text{m}$ median size cut with 1.5 GSD) and inspirable (ACGIH 1985) size ranges. The size distribution information could be used to estimate the regional deposition of the inhaled particles.
- B) Bulk sample of particle source. Bulk samples can be aerosolized for direct measurement by an aerodynamic classifier, the results of which can be treated as with mode A. The mechanism of particle dispersion to form the aerosol must be justified as being similar to the mechanism of accidental release. When there is reasonable justification, direct measurement of aerodynamic particle size eliminates many variables and provides much more reliable information. Measurement of the Stokes diameter particle size in a liquid would require some measure of particle density to estimate the aerodynamic size distribution from the Stokes diameter distribution. The least direct method would measure the geometric particle size distribution, which would require the measurement or estimation of particle density, dynamic shape factor, and specific activity distribution. A common problem with this type of measurement is the attachment of small radioactive particles to large nonradioactive particles, which results in a large particle of low specific activity. Deposition of this agglomerate in the respiratory tract is determined by the aerodynamic size of the whole agglomerate. All factors used to calculate the aerodynamic size distribution must be reported with their estimated confidence range values.

- C) Surface collection of samples. Particles collected on a surface must be removed from that surface before size analysis, unless the surface is suitable for direct electron microscopy. This mode of collection will often give only enough particles for geometric size analysis. Particle density, dynamic shape factor, and specific activity distribution must be measured or estimated in order to calculate AMAD and GSD. The method of geometric size analysis must be reported with the estimated values used to calculate the aerodynamic size distribution.

3.1.4 Acceptance and Interpretation of Results

Violation of any established criteria will disqualify a sample for acceptance of particle size measurement. Guidelines for the judgement of acceptability of a sample are to be included in the sampling protocol. For example, if only 20% of the activity can be washed off the collection medium, this cannot be accepted as representative of the original particle size distribution.

Some conditions of sample collection and analysis will influence the interpretation of measurements. The particle size measurement procedure will specify the factors to be reported with the results of measurement for each sample. The report should include a detailed description of sample collection, which includes an accurate drawing of the site of particle release and a description of the mechanism of dispersion. Use of these measurements for assessment of biological hazard is discussed in Chapter 5.0.

3.2 SUMMARY OF CRITERIA FOR PARTICLE SIZE MEASUREMENT

The main points of criteria for particle size measurement are summarized below. The criteria are listed separately for each of the three modes of particle collection:

A) Measurement by aerodynamic classification

- Ensure that the particle size distribution is representative of the potential exposure.
- Measure radioactivity as the relevant particle quantity in each size class.
- Use the same method to measure the activity on each stage of the size classifier.

- Ensure that the amount of material collected in the aerodynamic size classifier is within the allowable mass-loading of the instrument.
- Report the measured AMAD for a log-normal size distribution, along with GSD and the value of a statistical test of log-normality.
- Report the value of respirable fraction (% respirable) for measured log-normal size distributions and for size-selective samples.
- Establish acceptance criteria for each investigation; these should include the criteria listed above.
- Record confirmation that all established criteria have been satisfied for each investigation, or discuss the possible impact on experimental results of not meeting a particular criterion.

B) Criteria for size measurement of bulk sample

- Ensure that the size distribution of the sampled particles is representative of the potential exposure.
- If the bulk sample is aerosolized, apply the criteria for aerodynamic size classification [criteria A)].
- If an instrument which measures the Stokes diameter in a liquid is used, make a separate measurement of particle density to estimate the AED.
- If an instrument which measures the geometric particle diameter is used, apply an estimate of particle density and an estimate of the dynamic shape factor.
- Measure the specific activity of the material in the size range of interest.
- Assess the uniformity of the activity distribution throughout the size range measured.
- Include the values of particle density, dynamic shape factor, and specific activity in any report of calculated AMAD (GSD).
- Establish acceptance criteria for each investigation; these should include the criteria listed above.
- Record confirmation of all established criteria for each investigation, or discuss the impact on experimental results of not meeting a particular criterion.

C) Size Measurement of Surface Contamination

- Ensure that the particle size distribution is representative of the potential exposure.

- Prepare suitable collection surfaces for direct electron microscopy without transfer to another surface.
- If the particles are removed from the collection surface, the criteria B) apply to the sample.
- If the particles are removed from the collection surface, at least 90% of the activity should be removed.
- If the particles are removed from the surface, estimate the size distribution of particles remaining on the surface.
- Assess the uniformity of activity distribution throughout the size range measured.
- Include particle density, dynamic shape factor, specific activity, and methods of measurement in any report of calculated AMAD (GSD).
- Establish acceptance criteria for each investigation; these should include the criteria listed above.
- Record confirmation of all established criteria for each investigation, or discuss the impact on experimental results of not meeting a particular criterion.

4.0 COMBINATION OF DISSOLUTION AND PARTICLE SIZE MEASUREMENT

For *a priori* collection of samples, it is a fairly simple matter to collect separate samples for dissolution and particle size measurement; a particle size classifier can be operated during size-selective sampling for dissolution measurement. The two samples should represent the same airborne material. Material collected *a posteriori* may require that measurements of both particle size and dissolution rate be made from the same sample. Splitting a sample can easily bias the particle-size distribution between the two fractions. All the mechanisms involved in particle collection must be considered before attempting to split the sample into two representative fractions.

A posteriori sampling often requires geometric measurement of the particles with an optical method of detection. An alternative would be to resuspend the particles as an aerosol, and collect them with a size classifier. However, this process is difficult, expensive, and unreliable for small quantities of material, and is generally not justified. In the case of *a posteriori* samples, a fraction of the sample to be used for dissolution measurement may be the only available source of representative particles for size measurement. This will usually mean splitting a sample for the measurement of both dissolution rate and particle size distribution.

A common example of a sample which might be split for analysis of both dissolution rate and particle size is a nasal smear. This would be a wet sample with relatively little activity. Size measurement of particles from a nasal smear would be of limited value without accurate information of the airborne particle size distribution during the exposure. Particles deposited in the anterior nares would represent the large particle fraction and the ultra-fine particle fraction; the fine and intermediate particle sizes (0.1 - 15 μm) would not be well represented. Thus, the nasal smear particles would best represent the activity which would be swallowed to the stomach. Measurement of dissolution rate could be used to estimate f_1 for absorption from the gastrointestinal tract. Because the nasal smear does not have any well defined symmetry, it would be difficult to split a known fraction of the activity from the sample. Therefore, particle size distribution measurement

would be of tenuous value at best. The nasal smear would provide mostly qualitative information about the exposure.

4.1 SAMPLE-SPLITTING CRITERIA

The following guidelines should be used when splitting a sample and interpreting the results of its measurement.

4.1.1 Sample Collection and Handling

The amount of activity sampled and storage of the sample before measurement follows the same criteria as for individual measurements. Situations that require splitting of samples will often involve only limited amounts of activity. Thus, it will usually be necessary to use conservative preparation procedures.

4.1.2 Specifications of the Sample Splitting Procedure

Splitting of a sample must not bias the portion for dissolution measurement or the portion for particle size measurement. A filter sample may be simply cut in two through its center. In the case where a minimal amount of activity is involved, a smaller fraction of the filter could be used for particle size distribution measurement; a few hundred particles might be adequate.

4.1.3 Information to be Obtained to Apply the ICRP 30 Lung Model

The same information as specified above for measurement of dissolution rate and particle size distribution is to be provided for the ICRP 30 model. A split sample is likely to involve a number of assumptions and estimates. These must be fully described along with the calculation of particle size distribution.

4.1.4 Acceptance and Interpretation of Results

Violation of any established criteria will disqualify a sample for acceptance of dissolution and particle size measurement. Guidelines for the judgement of acceptability of a sample are to be included in the sampling protocol. For example, if a sample has no well defined symmetry, then it cannot be split into two portions of the same sample; two parts of the same sample medium may be treated as two separate samples.

Some conditions of sample collection and analysis will influence the interpretation of measurements. The procedure protocol will specify the factors to be reported with the results of measurement for each sample. The report should include a detailed description of sample collection, which includes an accurate drawing of the site of particle release and a description of the mechanism of dispersion. Use of these measurements for assessment of biological hazard is discussed in Chapter 5.0.

4.2 SUMMARY OF CRITERIA FOR SPLITTING OF SAMPLES

The main points of criteria for splitting of samples are summarized below.

- Splitting of the sample must not bias the measurements of dissolution rate or particle size distribution.
- The technique used on the split portion of the sample for measurement of dissolution must meet the criteria given above for dissolution rate measurement.
- The technique used on the split portion of the sample for measurement of particle size distribution must meet the criteria given above for particle size distribution measurement of the appropriate sampling mode.

5.0 EVALUATION AND INTERPRETATION OF PARTICLE MEASUREMENTS

The measurement of dissolution rate allows the placement of inhaled material or its components into one of the three retention classes, D, W, or Y, and the estimation of the value of f_1 . Clearance is a combination of dissolution and biomechanical clearance (transport by phagocytic cells and mucociliary clearance). The half-times of all these mechanisms are combined to yield an overall effective clearance rate. For short-term clearance (during the first few days after exposure) the effective half-time of clearance is dominated by dissolution in class D and dominated by biomechanical clearance in class Y. Between these extremes, clearance rate is determined by the combination of clearance mechanisms and dissolution rate. As defined in the ICRP 30 model, the clearance mechanisms are different for the various compartments (see Figure 1.2). Long-term clearance is strongly influenced by the dissolution rate of the material. Thus, dissolution rate half-time can be used to decide the retention class of the material. Divisions of the classes are arbitrarily chosen to be 10 days and 100 days dissolution half-time.

If the particles are known to be a discrete mixture of two different materials (i.e., any one particle contains only one form of the radionuclide of interest), then the inhalation exposure can be treated as two independent but simultaneous exposures. This would require extensive analysis (beyond dissolution and particle size analysis) to determine the relative fraction and size distribution of each component and is assumed not to be generally available. Hence, the particles are usually assumed to be a uniform mixture of the components (i.e., all components of dissolution rate come from each particle). Retention class is then assigned according to the weighted half-time, assuming that biomechanical is equal for both fractions of the inhaled material.

When two dissolution components of the particles are identified, the weighted half-time can be used to decide the retention class. For example, if the particles are found to have 40% of the activity dissolved with a half-time of 90 days and 60% dissolved with a half-time of 210 days, then the weighted half-time is $0.4 \times 90 + 0.6 \times 210 = 162$ days. Thus, the material is treated as class Y within the framework of the ICRP 30 lung model.

Dissolution in simulated gastric juice is used to estimate f_1 . The fraction of activity dissolved by day 1 should be a conservative value; *in vivo*, the particles are subject to the low pH for at most a few hours. Continued measurement beyond 1 day of dissolution gives more information about the dynamics of the dissolution, which may be used as a preliminary estimate of the dissolution in simulated lung fluid.

6.0 NEW MODEL OF LUNG CLEARANCE PROPOSED BY THE ICRP TASK GROUP

The clearance model shown in Figure 6.1 is being proposed by the ICRP Task Group that is reviewing the Lung Model for Committee II (Bair 1989). This model is proposed to replace the compartmentalized structure and fixed classifications of transportability incorporated in the current ICRP 30 model. The new approach is fundamentally different in that it treats biomechanical transport of materials within the respiratory tract and absorption of radio-nuclides into the blood as independent processes that act strictly in competition with each other. Thus, a given material is assumed to be absorbed into the blood at the same fractional rate from whatever part of the respiratory tract in which it happens to reside. The amount absorbed from each region is then determined by the length of time that particles reside there, and thus by the competitive action of a mechanical clearance rate and a fractional rate of absorption. The mechanical clearance rate in each region is a characteristic of the subject; the fractional absorption rate is purely a characteristic of the material. The proposed model is structured mathematically to represent the variation with time in rates of both mechanical particle clearance and absorption that is observed in practice.

This more mechanistic representation of particle clearance behavior in the respiratory tract will avoid many of the difficulties engendered by forcing a material into a retention class within the framework of the ICRP 30 model, and then expecting the model to predict correctly the effect of aerosol size on regional distribution and absorption rates. The value of the AMAD will be used to calculate the regional distribution of deposited activity. Absorption is then integrated through the time of clearance from all regions of the respiratory tract, based on the value of the dissolution rate. For sparingly soluble materials, the proposed model will automatically determine that the amount of activity translocated to the blood is strongly influenced by the site of deposition within the respiratory tract, and thus by the size distribution of the inhaled aerosol. Furthermore, the fractional absorption rate that is applied to material in each region is related more directly in the proposed model than in the current model to the rate of dissolution and its variation with time, which would be observed *in vitro* in a well designed dissolution test carried out on a sample of the inhaled material.

FIGURE 6.1. Proposed Model of Clearance from the Respiratory Tract. Symbols indicate fractional rates of clearance, at time t after an acute intake, by each route from each region: extrathoracic (ET), tracheobronchiolar (TB), alveolar-interstitial (AI); where $s_i(t)$ is the rate of translocation to blood from region i $g_i(t)$ mechanical clearance towards the GI tract, $l_i(t)$ mechanical clearance towards regional lymph nodes, and $x_{ET}(t)$ is extrinsic clearance from the ET region.

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APPENDIX A

DECISION SCHEME TO DETERMINE TOTAL SAMPLE SIZE

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There are many factors that affect the best choice of sample size in terms of total activity and mass. Solubility of the material matrix is the most important parameter. Then, for a given solubility, specific activity is another important parameter. If the radionuclide is distributed through a large mass of matrix with low specific activity, a large amount of the material must dissolve to release a significant amount of activity. Thus, solubility and specific activity directly contribute to the dissolution rate of the radionuclide. Another important factor is the specific surface area of the sample (not considered in this scheme). A finely divided powder presents a substantially greater surface area to the solvent than does a coarse powder, resulting in faster dissolution. Specific surface area can only be measured with a special apparatus dedicated to this purpose which is not commonly available. A crude value for specific surface area can be estimated from the size distribution of the particles.

Quantitative measurement of dissolution rate should be preceded by preliminary measurements of solubility and dissolution rate, unless the source material is known with enough certainty to assume its solubility character. Specific activity of a powder can be measured by weight and total activity of a sample; it is important that this powder be of representative particle-size distribution. The scheme shown in Figure A.1 is intended to be only a rough guide when choice of sample size is to be made. Extreme values of specific activity, specific surface area, or solubility might substantially influence the choice of sample size for measurement of dissolution rate.

FIGURE A.1. Decision Scheme for Choice of Total Sample Size

APPENDIX B

DECISION SCHEME TO DETERMINE THE DISSOLUTION MEASUREMENT SCHEDULE

APPENDIX B

DECISION SCHEME TO DETERMINE THE DISSOLUTION MEASUREMENT SCHEDULE

A fraction collection schedule needs to be established for each sample. If the character of the sample material is known in advance, then a tentative schedule may be planned, with checks at each fraction for the suitability of the schedule. If the solubility of the sample is unknown, then the fraction collection schedule will have to be decided as the dissolution progresses. This is based on knowledge of the chemical solubility of the material and total activity of the sample, which must be determined or estimated in advance. If dissolution results in a percent saturation value S exceeding 10%, then the sample should be discarded and dissolution started over with a smaller quantity of material. The activity in terms of percent total sample activity (A) is also used to decide the fraction collection schedule for acquisition of as much information as reasonably possible. Determination of S may involve chemical analysis of the solute which may have to be retrospective. In such a case, it would be safest to keep A at the lowest practical value in order to minimize S and avoid exceeding 10% of the saturation value. The following decision scheme as a logical path is a suggested format:

<u>Collection Time</u>	<u>Logical Decision</u>
hour 1	if $S > 10\%$ then hour 2 ^(a) if $A > 10\%$ then hour 2 if $A < 1\%$ then day 1 else hour 4
hour 2	if $S > 10\%$ then start over if $A > 10\%$ then hour if $A < 1\%$ then day 1 else hour 8

-
- (a) This brief description is a conditional proposition that can be expanded to read "if the value of S is greater than 10% then collect the next fraction at hour 2." When the condition is not met, the next conditional proposition is tested.

hour 4	if S > 10% then start over if A > 10% then hour 8 else day 1
hour 8	if S > 10% then start over else day 1
day 1	if S > 10% then start over if A > 10% then day 2 if A < 1% then day 10 else day 4
day 2	if S > 10% then start over if A > 10% then day 4 else day 10
day 4	if S > 10% then start over else day 10
day 10	if S > 10% then start over if A > 10% then day 20 if A < 1 % then day 100 else day 40
day 20	if S > 10% then start over if A > 10% then day 40 else day 100
day 40	if S > 10% then start over else day 100
day 100	if S > 10% then start over if A > 10% then day 200 if A < 0.1% then stop else day 300
day 200	if S > 10% then start over if A < 0.1% then stop else day 300
day 300	if S > 10% then start over else stop.

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