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POTENTIAL HAZARDS AS A RESULT OF INHALATION OF RADIOIODINES: A LITERATURE SURVEY

by
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Bioenvironmental Research Program
Southwestern Radiological Health Laboratory
U. S. Public Health Service
Department of Health, Education, and Welfare
Las Vegas, Nevada

January 5, 1966

This study performed under a Memorandum of Understanding (No. SF 54 373)
for the
U. S. ATOMIC ENERGY COMMISSION

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I. INTRODUCTION

This report gives a brief survey of some of the existing literature relative to the subject of potential hazards to man which might result from releases of radioiodines into the biosphere. The related topic of potential hazards from ingestion of radioiodine is also touched upon since the determination of total hazard to man must be the ultimate goal of any research program which has been designed to assess the overall public health significance of any radioiodine releases. There has been a general assumption on the basis of limited data that the ingestion hazard is such that any concurrent inhalation hazard would be of negligible significance. No issue will be taken with this assumption. Rather this report will attempt to survey the present state of knowledge on the subject of potential radioiodine inhalation hazards in an effort to identify specific areas in which additional research is required, either to fortify the usual assumptions or to determine under what conditions they might be invalid. For the sake of brevity, an exhaustive discussion of each subject considered is not attempted. For amplification of any specific topic the reader is encouraged to consult pertinent references given at the end of the report.

It is impossible to investigate every facet of radioiodine fallout in detail,[3] nevertheless, a systematic and well organized approach to test a hypothesis that there is an inhalation hazard of radioiodines to man is feasible because radioiodine has a relatively high percentage of release among fission products, an appreciably high fission yield, and is biologically available to man and animal. Accurate exposure and dosage determinations are required for establishment of radiation protection procedures and maximum doses. To make these determinations,

with regard to inhalation of radioiodines, answers to the following questions should be useful:

1. What are the potential sources of atmospheric radioiodine contamination?
2. What are the chemical and physical properties of the radioiodines and the conditions of their release, e.g., gaseous, particulate, fractionation?
3. What is the particle size distribution inhaled by the animal and biological fate of each size?
4. What fraction of the intake of radioiodines is retained in the body following inhalation?
5. What is the deposition, retention, translocation, and elimination of inhaled radioiodines in normal physiological states?
6. What is the distribution of radioiodines in specific tissues and organs of various species of animals?

The scope of this report, other than for limited information of potential sources and physico-chemical aspects of the radioiodines, is primarily confined to questions 5 and 6. The discussion will attempt to expose areas of paucity in research on radioiodine inhalation and thereby hopefully serve as a reference in any contemplated inhalation studies in the field or in the laboratory.

Following the discussion of the literature, research problems will be suggested, keeping in mind that a research program on inhaled radioiodine is universally concerned with the fate and effects of the inhaled radioiodine directly and indirectly upon nearly all mammals, especially man.

II. POTENTIAL SOURCES OF RADIOIODINE

A. INTRODUCTION

Radioiodines released into the atmosphere and available to the pulmonary system may be a hazard only under specific pertinent conditions existing at the time of release. Biological availability will depend on such physical factors as the source of the radioiodines, the proximity of the source to the population, and meteorological conditions existing before and after release.

Most nuclear reactors maintain high inventories of radioiodines. The quantity, for the most part, is dependent on the thermal power and the length of operation of the reactor. Under normal operating procedures the radioiodines reach equilibrium and are contained for a predetermined time to allow for radioactive decay to take place. However, if an accidental release of fission products should occur, the Health Physicist would have to determine the amount of radiation to which the surrounding population would be exposed. Accidental releases can occur from direct exhaust from faulty reactor assemblies, off gases, and uncontained accidental criticality. These nuclear reactor accidental releases can normally be quantitated more accurately than releases from nuclear devices following detonation.

Nuclear weapons detonated in the atmosphere may release large quantities of radioiodines; however, the levels or concentrations of radioiodines observed under different conditions will be extremely variable. The measured radioactivity is often orders of magnitude different from predicted values. Inhalation of radioiodines by livestock following nuclear weapon detonation has been considered to be of no major importance.[31]

Underground nuclear explosions are normally contained underground unless cratering is planned. Following underground detonation, the volatile elements of which radioiodines are representative, may be inadvertently released into the atmosphere. The release of the volatile elements could become a very acute inhalation problem especially with the release of large quantities of short-lived radioiodines.

One major area of importance lies in the chemistry and physics of radioiodines in the gas and aerosol formation preceding and following release to the atmosphere from nuclear fission reactions. Little is known about the transport of these elements in the biosphere, and less is known quantitatively about inhalation of radioiodines from field sources than any other aspect of radioactivity resulting from nuclear fission reactions.[16] A brief discussion of potential sources of radioiodines will be presented with reference to specific conditions which allow radioiodines to become biologically available. A comprehensive coverage of each subject is considered to be beyond the scope of this report.

B. NUCLEAR REACTORS

A major contributing source of radioiodines to the atmosphere is the nuclear reactor. In general, all nuclear reactors, regardless of size or shape, are composed of the fuel moderator, reflector, blanket, controls, cooling system, cladding, reactor vessel, radiation shielding, radiation monitoring system, and containment mechanism. Further details on reactor construction and fission reactions can be found in any nuclear science textbook.[55]

Low power auxiliary units, as opposed to primary propulsion reactors such as the Kiwi, possess similar characteristics that may be considered uniformly for all hazard estimates. These may differ

in parameters such as type of fuel, cladding, and operating time or temperature; however, the actual levels or quantity of radioiodines produced within the reactor will be dependent mainly on the power level and the operating time. Once a release occurs, the ensuing transport and diffusion of fission products are usually considered to be uniform for all proposed units since the physico-chemical nature of the products depends more on release conditions than on reactor type.[92] The increasing use of low power auxiliary units increases the probability that more fission products will be released into the atmosphere due to inherent problems of containment.

In contrast, power producing reactors such as the Calder-Hall type may have leaks in the containment mechanism or have fission product leaks into the cooling gas from faulty fuel elements. In such cases, fission products are usually discharged into the environment in significant quantities only during the release of the CO_2 coolant following reactor shut-down.[98]

Irrespective of reactor type, fission products will normally be released in large quantities from the destruction of fuel material. In fuel element melting experiments, which were designed to simulate core meltdown during an uncontrolled nuclear excursion or other similar accident conditions, iodine and rare gas isotopes were released from the core in higher percentages than other fission products.[25] This is to be expected since Roberts[98] found that fission products are retained almost entirely within the high temperature zone with the exception of noble gases, iodine, cesium, and tellurium, and, if oxygen is present, ruthenium.

Another possible source of radioactivity that might become biologically available is the activation of particulates present in the operating region of a reactor. These particulates could be from construction

materials such as cement, sand, and dust within the reactor area. If these are allowed to escape to the outside atmosphere, it would probably be found that the particles would have the normal size distribution associated with corrosion products of construction material dust.[42]

1. Levels of Radioiodine in the Atmosphere

During the design of a nuclear reactor, guides to maximum permissible concentrations of ^{131}I must be considered. Barry[14] listed permissible concentrations of ^{131}I that were meant to serve as guides to reactor designers and were not intended for normal health physics control levels. Griffiths and Erickson[56] reported that prior to the assembly and operation of a reactor at the Nuclear Rocket Development Station (NRDS), an analysis is prepared to determine safety characteristics of the reactor including evaluation of reactor effluent release for planned operations and for creditable accidents. For a normal test the gross fission product release is assumed near 5% with radioactive iodine release values of 1 - 6%. Calculations for determining the thyroid dose contributed by inhalation of radioiodine released during reactor operations are usually based on the Sutton model for atmospheric diffusion.[10]

In predicting the thyroid dose, it is most difficult to relate the degree of absorption or adsorption of the radioiodines to various sized particles. However, those particles whose diameter is above the respirable range may be considered relatively unimportant in contributing to the thyroid dose resulting from inhalation only.

Since it is possible that inhalation of radioiodines could be a hazard, the primary objective of an environmental monitoring

program should be to establish, within reasonable confidence, that the radiation exposure received by individual members of the general public will not exceed specified safety levels. Measurements intended to serve this purpose should, therefore, be capable of being related to these levels. Levels of radioiodines released into the atmosphere will usually depend on the type of reactor release that occurs. Whether the release is from one time releases, from nuclear reactor accidents or emergencies, or from continuous routine reactor operation, the quantity of the radioiodines is reduced by two processes--radioactive decay and diffusion.

2. Radioactive Decay and Diffusion

Radioactive decay for radioiodines can be predicted with considerable accuracy (See Table 1). Knowledge of the decay scheme is extremely important in dose determinations following release, especially if short-lived radioiodines are being considered. When computing dose determinations for radioiodines released as fission products within close proximity of the release, rate of radioactive decay plays a major role. Dolphin and Beach[35] used one hour post release time conditions in calculating the relative hazard of the significant iodine isotopes (^{131}I, ^{132}I, ^{133}I, ^{134}I, ^{135}I) following accidental release of fission products from criticality incidents or from irradiated reactor fuel elements. One hour was chosen because it was thought that no appreciable amount of fission product activity could be released, become airborne, subsequently inhaled, and concentrated in the thyroid in a shorter time. It is apparent that the greater the elapsed time following release, the greater is the ^{131}I contribution to a possible hazard (See Table 2).

Diffusion, however, is not as simple to calculate as decay rate because of the vast number of parameters, such as particle

size, particle density and composition, velocity of wind, wind shear, temperature gradients and topographical features. These are seldom known with sufficient accuracy at the precise time of radioiodine release. Predictions are usually poor estimates at best. For example, prediction of the air concentrations following the SL-1 accident (80 curies of ^{131}I released) were in reasonable agreement with measured air concentrations of ^{131}I up to several miles around the reactor, but predicted values were a factor of ten or more lower than the measured values at distances beyond fifteen miles.[69]

C. WEAPONS DEVELOPMENT TESTS AND PLOWSHARE EXPERIMENTS

The biological availability of the radioiodines (^{131}I to ^{135}I) depends on many physico-chemical interactions as well as meteorological conditions, type of detonation and fission yield. The interactions of the latter three conditions have been well documented in "The Effects of Nuclear Weapons"[43] and are beyond the scope of this paper.

1. Weapon Development Tests Conducted Above Ground

Rates and mechanisms of distribution and transfer of radioiodines in the atmosphere from low yield detonations are of more concern to the problem of inhalation as a possible hazard than are high yield detonations. This is understandable since it is generally true that tropospheric contamination is greater, local fallout is less, and external exposure is reduced to within a narrow band in high yield detonations. The very close-in local fallout is of no concern here because large particles measuring more than 30 microns, even though they contain roughly 80% of the radioactivity, are not within the respirable range. However, the

ten microns in diameter particle, settling velocity of 0.845 cm/sec, contains the highest percentage of biologically available elements and will be deposited or suspended within a narrow band outside of the heavy local fallout area.[73] Outside of the heavy local fallout implies that the external dose is negligibly small and arrival times are measured in hours. This period of time is sufficiently soon after detonation for short-lived nuclides, i.e., half-lives less than one day, to be present.

The quantities of biologically available fission products may vary in the air and on surfaces due to fractionation. The phenomenon of radionuclide fractionation following nuclear explosions complicates the attempt to define contamination surface density in precise terms because the composition of each particle may vary, i.e., a profile of different biologically available fission products may be developed.[49] This profile of available fission products, of which the radioiodines are representative, may present a high percentage of biologically available radioiodines to the pulmonary system during intervals following detonation of a low yield nuclear explosion. Clark,[20] attempting to simulate a realistic fallout environment for a land surface nuclear detonation, utilized a simplified mathematical fallout model to estimate:

a. Fallout particle sizes.
b. Deposited mass per unit area.
c. Standard radiation intensities as functions of downwind distance of weapon yields from 1 KT to 100 MT.

2. Underground Nuclear Explosions

Underground nuclear explosions of Plowshare experiments and weapon development tests are usually designed to be contained, although they are capable of causing cratering with substantial release of radioactivity, especially radioiodines, into the atmosphere.

Containment of the radioiodines will depend in part on the nature of the soil structure of the medium where the detonation takes place. Presence of seams, faults or fractures of the medium and estimation of the nuclear yield must be considered. If an inadvertent release occurs, the most gaseous and volatile elements appear to be restricted to the lower layers of the troposphere.

Following an underground cratering explosion of 0.42 kiloton, Nordyke and Wray[93] reported a base surge cloud which rose to an altitude of about 8000 feet and was 15 to 20 miles in width at a distance of 75 miles downwind. Seventy miles to the north of the detonation site, an atmospheric concentration of 576 picocuries per cubic meter of radioiodine was observed.[114] Data obtained following a large nuclear excavation (Sedan) showed that the fallout pattern was clearly asymmetrical.[57] There was a steep gradient, a "hot line" and a feathering out of fallout. All were consistent with shearing of the upper portion of the cloud. The moving debris and the widespread nature of a fallout pattern usually complicate the evaluation and interpretation of data leading to uncertainties as to the mechanism of transport of radioiodines through the biosphere.[67] Dunning[40] reported that relatively high concentrations of fallout material are found in the air for only a few hours and essentially all of the calculated intake by inhalation is completed within 24 hours following low-yield detonations. This band of high atmospheric specific activity, apparently within the respirable range, is of importance in evaluation of inhalation hazards of radioiodine.

Martell[81] stated that the only practical procedure for assessing the extent of an inadvertently released radioiodine and other radioactivity products appears to be the direct measurement of the

escaping clouds and vapors for each individual event. Likewise, it appears that a practical approach for assessing the extent of the hazard from inhalation of radioiodines is having knowledge of deposition, retention, translocation, and secretion of radioiodines in individual animals, man included, at the time of cloud passage for each individual event.

III. TRANSPORT OF RADIOIODINES FROM SOURCES TO BIOSPHERE

A. INTRODUCTION

Iodine has an atomic number of 53 and 24 isotopes which range from 117 to 140 atomic mass units. Iodine-127 is the only stable isotope of the iodine family. Since ^{127}I is not radioactive it will not be discussed in the mechanics of transport, but will be included in the discussion of translocation of inhaled radioiodines. The physical half-lives of the remaining isotopes vary from approximately 1.5 seconds for ^{140}I to 1.6×10^{7} years for ^{129}I. Relative yields of these isotopes from fission of ^{235}U or ^{239}Pu are shown in Table 3. The quantities, in curie amounts, following 10^{20} instantaneous fissions of ^{235}U, as well as the quantities remaining after a period of time, are given in Table 4. Decay sequences for ^{129}I, ^{131}I to ^{135}I are listed in detail in Table 1.

Because of the relatively short half-lives of ^{132}I, ^{133}I, ^{134}I and ^{135}I, these isotopes appear to have received inadequate consideration for being possible contributors to the total radiation dose. Although inhalation of these isotopes has not generally been regarded as extremely hazardous, the possibility always exists that a release could cause some segment of the population to be exposed to large respirable quantities of these radioiodines. The circumstances of release and, therefore, exposure of the population to radioiodines has normally been such that ^{131}I, for the most part, overshadowed the importance of the other iodine isotopes as the radiation hazard most commonly encountered.

This section of the report will deal only briefly with the physico-chemical properties of the radioiodines. In particular, physical and

chemical forms, particle size distribution and transport will be discussed with reference to biological availability to the respiratory tract.

B. CHEMICAL STATES OF RADIOIODINES USUALLY OBSERVED

Iodine can undergo rapid chemical transformations as well as physical changes. Megaw and May[88] showed that approximately one hour following release of elemental I_2 in the Pluto reactor shell, 40 to 80% of the airborne iodine was associated with particulate material. Much of the iodine vapor changed from the elemental form to unidentified gaseous species during their experiments of 3 to 5 hours duration. In vapors, such as above and others released in reactor shells of various types and from nuclear explosions, the volatile forms are found as elemental I_2, as inorganic vapors, as organic vapors (methyl iodide)[44] and as many oxidized states[65](See Table 5). Perkins reported[97] that experiments on gaseous effluents from the Hanford chemical separation plant indicated that less than 0.3% was in the particulate form. Iodines leached from the particulate material were shown to be about 66% in the reduced state (I_2 or I^-), about 33% in the iodate form, and less than 5% in the periodate form. The data, according to Perkins, suggested that ^{131}I released into the atmosphere does not immediately adsorb on particulate material in the air and even several miles away may still be in a gaseous state (See Table 6). The gaseous form varied from 10 to 90% of fallout from plant emission.

C. PHYSICAL STATES OF RADIOIODINES USUALLY OBSERVED

Particle sizes, upon which radioiodines are adsorbed or absorbed, depend on the origin of the particulate matter. In the heating of irradiated uranium, Gallimore and Mercer[50] found some form of ^{131}I was carried on particles of peak diameters of 15 Å and 60 Å. Approximately 10% seemed to be a gas or vapor. Karioris et al[71] found that particle size distribution is multimodal when two or more chemical species are

present in aerosols when studied in an exploding conductor aerosol generator. Particle sizes resulting from the heating of UO_2 to 400°C, 600°C and 800°C and subjected to a 8.3 centimeter per second air-stream, were found to be within the 2 to 5 microns diameter range 20 inches downstream from the UO_2 source.[21] Under similar conditions, but with the UO_2 heated to 1200°C, the particles measured 0.015 to 0.5 microns in diameter. It is probable that particulate size depends on the temperature of the fuel and the amount of air flow over the heated fuel. The form and amount of iodine found on particulates appears to be influenced accordingly.

Distribution of particulate size following nuclear explosions will, among other factors, depend on the type of detonation and total fission yield. Following a land surface shot, roughly 80% of the radioactivity will be in particles greater than 30 microns in diameter. On the other hand, these particles are not primarily within the respirable range of interest and are not included in this discussion. The particles less than 20 microns are carried into the atmosphere and their motions are normally determined, because of their MMD (mean mass diameter) and weight, by atmospheric motions rather than by gravitational fall.[66] If the shot does not intersect the surface of the earth, as in an air burst, the spectrum size of particulates averages approximately 3 microns in diameter. With increased yield and height of burst, the particle size may shift to much smaller diameters.[73] Irrespective of type of detonation, the chemical states of the radioiodines and, therefore, absorption or adsorption on the particulate matter, may be independent of the origin or environmental history.[72]

Because of the variances that normally exist, Holland[66] feels that it is very difficult to conduct realistic experimental research on radioiodine behavior in fallout. Nevertheless, it is necessary to develop

realistic experimental procedures regardless of difficulties encountered because not only is there the requirement that the distribution and chemical state of the radioiodines in or on these particle sizes be known, but also there is a requirement to know the particle size distribution. The extent to which the radioiodine is physically incorporated within the particulate matter, whether it be dust, fuel material, etc., may affect the participation in chemical or biochemical reactions and possibly have an importance equal to or greater than the specific chemical form in which it exists in the particle.[74]

It is a well known fact that a dust suspension, such as that caused by a nuclear excavation or emitted from nuclear reactor stacks, continually undergoes a change with respect to the particle size distribution and percentage of particulate matter containing ^{131}I. Agglutination, sedimentation and impaction can be considered to cause this instability of a suspension.[32] These phenomena complicate the problem of calculating and predicting the quantity of radioiodine that is carried on the surface of a carrier dust from the point of release. The radioactive particulates after being collected by conventional means show a total radioactivity deposition that bears no simple predictable relationship to the mass deposition. Since an aerosol cloud will act as a carrier for the transport of radioactive material into the respiratory tract, the radioactivity per mass of particle or the ratio of the quantity of adsorbed activity per respirable particle of the aerosol must be considered in computing the radiation dose. The particle size will determine the behavior of the aerosol and the quantity of radioactivity will determine the contribution of the inhaled dose.[26]

The chemical forms and solubilities of the radioiodines greatly influence their deposition on particulate matter and hence their absorption in the biological systems. Keisch and Koch[72] stated that, after

studying ^{131}I leached from fallout, their results implied that the rate at which the leachable ^{131}I was removed was not dependent on the chemical state in which it existed in the particulate phase. They further stated that the dissolution of a sparingly soluble material in which the radioiodine was adsorbed was more likely to be the rate and equilibrium determining factor for the leaching mechanism. This is not surprising since it is known that iodine reacts with many materials and as a halogen is usually found with valences ranging from -1 to +7 (See Table 5). Therefore, it would be expected to dissolve in water droplets to form iodide (I^-), iodate (IO_3^-), and periodate (IO_4^-) ions. Leach yields have shown 65.5%, 29.5% and less than 5% for the iodide, iodate and periodate states respectively.[72,97] The chemical form of approximately 60% of the ^{131}I remaining in the particles after leaching was not determined.[72]

The author is of the opinion that the present state of knowledge of the transport of radioiodines through the biosphere can be summed up rather quickly by quoting the summary from a paper presented by Holland in 1963.[65] He stated:

> "The only conclusion which can be drawn at this time regarding the partitioning of I^{131} between vapor and particulates, between soluble and insoluble forms and among elemental, reduced, and oxidized states is that none is clearly dominant over any great range of conditions."

IV. INFLUENCE OF CERTAIN RESPIRATORY MECHANISMS ON DEPOSITION, RETENTION, CLEARANCE AND TRANSLOCATION OF INHALED RADIOIODINES

A. INTRODUCTION

A major and, under special conditions, possibly the most important route for entry of radioiodine into the body is by inhalation. Langham[78] listed seventeen different variables that affect the deposition, retention and translocation of particulate matter in the respiratory tract. Some of these parameters are particle size and shape, solubility, hygroscopicity, wetting, concentration, respiration rate, particle density, flocculation, chemical nature or form, and inspired and expired air flow rate.

Of the above, particle size has received the most attention and has been investigated both experimentally and theoretically. Langham[78] reported that Stannard attached special significance to the possibility that a large fraction of the total radioactivity introduced into the atmospheric environment may be associated with a number of particles and not with mass concentration. However, the minimum in the mass retention curve may be severely misleading with regard to lung retention of radioactivity unless specific activity is considered. He further stated that this aspect of the potential inhalation hazard is worthy of continued investigation. Emphasis on respiratory gas exchange, diffusion, distribution of ventilation, perfusion and mechanics of respiration is required for a more rational approach to an ideal lung model. It is important to be able to predict the time-rate of respiratory uptake and internal transport and body storage of absorbed gases if there is ever to be a basis on which to relate the effective toxic dose at critical sites within the body to the atmospheric concentration and time pattern of exposure.[64]

This section will cover deposition, retention, translocation, and excretion of radioactive materials, particularly the radioiodines. Deposition will be discussed with reference to vapor or particulate matter deposited in various regions of the respiratory tract. Retention will be concerned with the percentage of the radioiodines remaining and the mechanisms of removal from the lung. Translocation will deal with the mobilization of the iodines into the critical organ, assumed to be the thyroid. Discussion of the thyroid will be in detail since the end result of inhalation of radioiodine is normally assumed to be thyroid damage. A brief statement of the up-to-date pathological findings will be included.

B. DEPOSITION: INFLUENCE OF PHYSIOLOGICAL FACTORS

1. Upper Respiratory Tract

Flow of air into the lungs must enter through the oral or nasal cavities and proceed down the trachea into the bronchi to reach the pulmonary lobules. When nasal breathing is predominant, deposition of particulate matter of 1 - 3 microns is noted in the alveoli.[46] Beyond this range, deposition diminishes with decreasing particle size to 0.1 micron, then Brownian motion tends again to increase deposition. Practically all particles of over 10 microns are filtered out at this level. Nasal absorption of vapors such as Sarin was shown to be 98% in the rabbit, 93% in the monkey and 96% in man.[2] In oral breathing, deposition in the alveoli is minimal at 0.5 micron and increases for both smaller and larger particle sizes. Oral inhalation of Sarin vapor showed that a significant portion of the gas reached the bronchial tree, particularly at rapid flow rates. Flow rate is the velocity with which the air enters or leaves the lungs and airways during the act of breathing. The inspiratory and expiratory flow rates and resistances can be represented by

flow curves developed by measuring instantaneous flow as a function of time. Silverman[105] reported development of a linear-response flow meter that records instantaneous changes in air flow during inspiration and expiration. He reported a new concept of respiratory work rate and the information obtained can be used for study of deposition of aerosols in various collecting devices under pulsating flow. As the air enters the bronchi, partial mixing of the gaseous stream occurs. Flow may be laminar or turbulent, depending on velocity. In the segmental bronchi, there are many large pulses of flow that are synchronous with the heart beat.[117] Drasche[37] demonstrated that the inspiratory velocity pattern was predominantly dependent on constitutional factors such as tension, anxiety, fear, etc.

Conduction of streams of gases and vapors is through the so-called anatomical dead space. This space is defined as the internal volume of the conducting airway from the nose and mouth down to but not including the alveoli. By definition, the anatomical dead space is a conducting system to the alveoli; therefore, no gas exchange is accomplished in this space. In this discussion the expression respiratory dead space will include "anatomical" and "physiological" dead space. Both components normally vary with tidal volume.[104, 113] Variations that are observed in tidal volumes during measurements of the dead space might represent unperfused alveoli that are ventilated,[122] or too much air reaching the alveoli in proportion to their capillary blood flow.

During movement of streams of gases, the removal of particulate matter down to and including the terminal bronchioles is observed to be 100% of particles over 10 microns in diameter and

80% of particles over 5 microns in diameter.[62] However, there are significant differences in the uptake of dust particles smaller than 5 microns in healthy subjects (man) with equal lung volumes and equal ventilation capacities. The total transit time for air, and probably particulates, from the mouth to the alveolus is directly proportional to the length of the bronchial airway supplying the alveolus.[101] This transit time, determined by breathing frequency, greatly influences the deposition rate. As the breathing frequency decreases, deposition of particles with diameters of 1 to 2 microns increases.[62]

2. Lower Respiratory Tract

Below the terminal bronchioles are the respiratory bronchioles, atria, alveolar ducts and alveoli; together they make up the pulmonary lobule. This area of the lung, the distinct anatomy depending on the species,[75,85] is where rapid gas exchange occurs. Hatch[62,63] reported that the highest probability for particle deposition in the pulmonary lobule occurs in the range of 1 to 2 microns where precipitation by diffusion takes place. Within 0.25 to 0.5 micron particle diameter, the combined forces of precipitation by gravitation and diffusion are minimal and, therefore, have the lowest probability for deposition in the lobules. Particles below 0.25 micron average diameter are deposited mainly by diffusion. (See Figure 1 and Table 7). For the most part, deposition of particles less than 0.1 micron is limited only by the fraction of inspired air that goes to the lungs.[62]

3. Lung Volumes and Capacities

Lung burden estimates from particle deposition cannot or should not be made without knowledge of the lung volumes (essentially anatomical measurements) and pulmonary ventilation

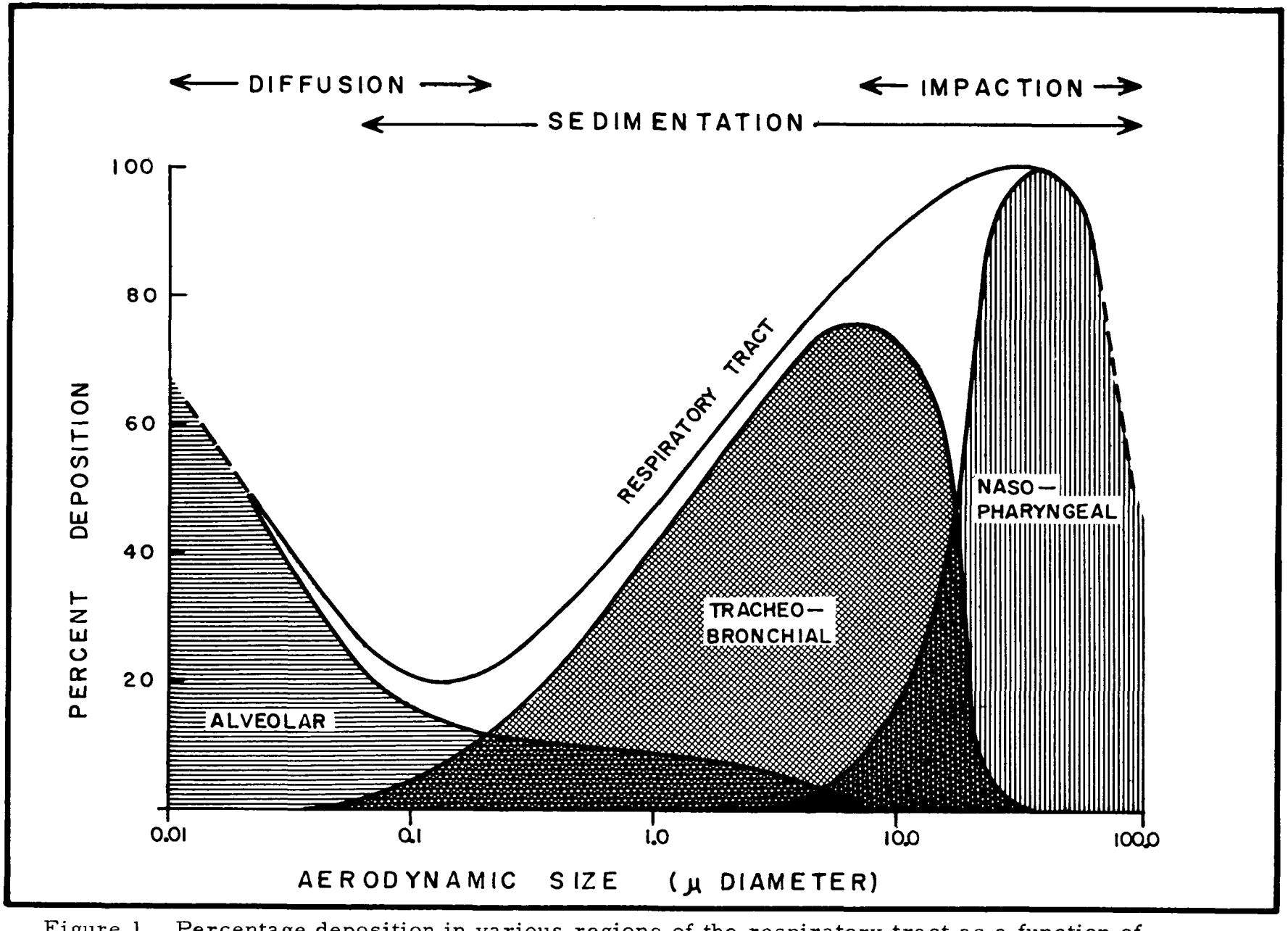

Figure 1. Percentage deposition in various regions of the respiratory tract as a function of aerosol particle size; unit density spheres assumed.

(a function measurement). Lung volumes and capacities are defined in Table 8 and Figure 2. Residual volume, inspiratory reserve volume and expiratory reserve volume are only static volumes, whereas tidal volume is dependent on mechanics of inspiration and expiration. Because pulmonary ventilation is a dynamic process, quantitation of air movements through the conducting airway to the alveoli is necessary to be able to calculate the alveolar ventilation rate, i.e., the volume of air reaching the alveoli per minute. The volume of pulmonary lobule ventilation is, therefore, primarily dependent on frequency of breathing, tidal volume, and amount of respiratory dead space. The degree of alveolar ventilation will normally be reproducible in the same animal as long as pulmonary pathology does not exist. The amount of ventilation per alveolus will differ in the various species and with the frequency of breathing of a particular subject. The rate of breathing will influence differences in relative distribution of the dead space gas.[101] (See Tables 9 and 10). Although the overall pressure gradient to all alveoli is usually regarded to be about the same, differences in transit time are observed. This leads to differences in effective ventilation of alveoli even though total ventilation of all alveoli is the same. It is therefore logical to assume that all alveoli do not necessarily contribute to the expired air simultaneously.

Total and effective ventilation of the lungs depends on numerous physiological and anatomical features of the species under study. Two animals of equal body size may have lungs of the same vital capacity, but if one of these animals has a higher rate of metabolism, the alveoli of the lung will usually be smaller, as the size of the alveoli appears not to be always related to the

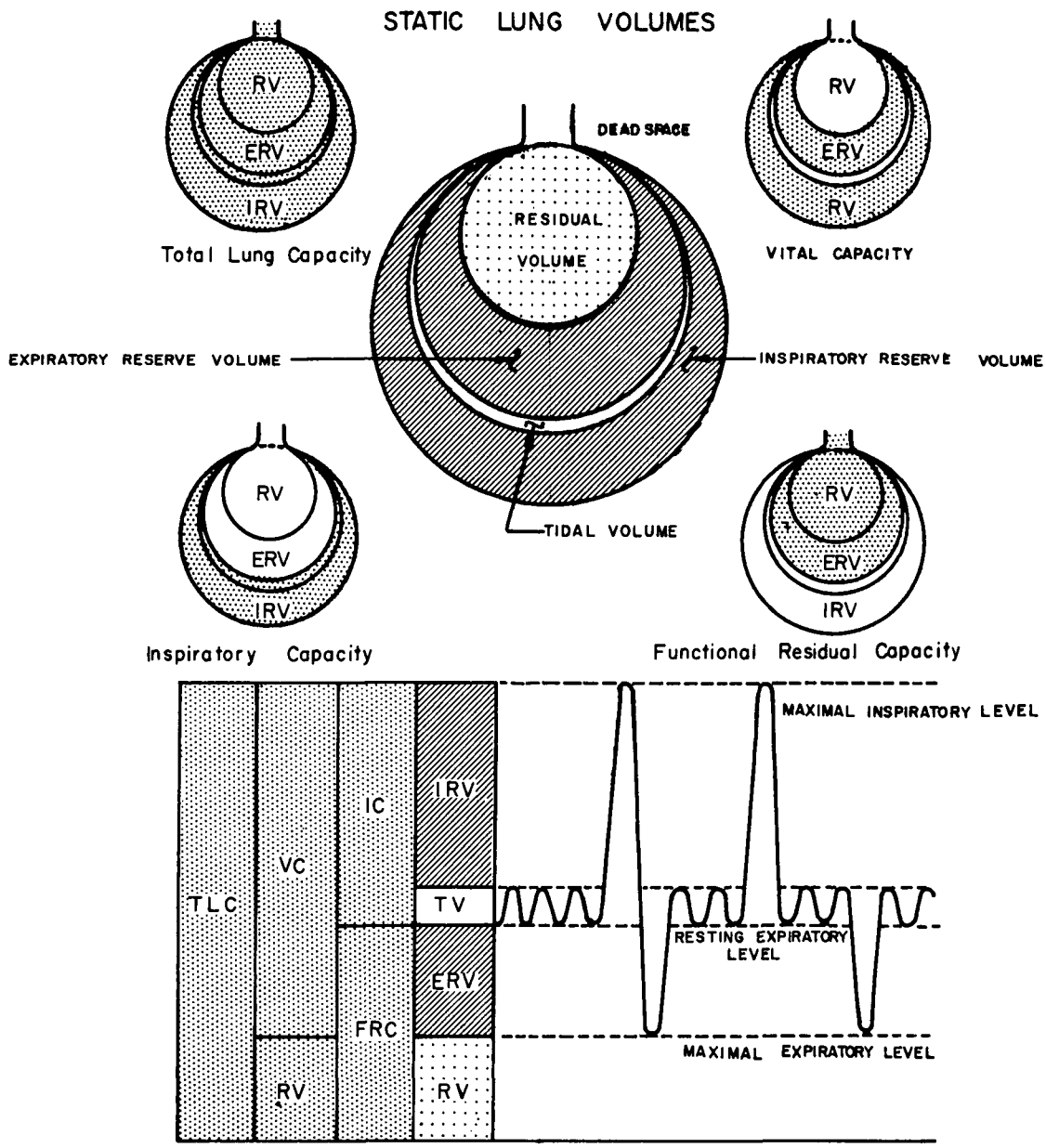

Figure 2. Lung volumes. (Courtesy of Year Book Medical Publishers, Inc. and Dr. Julius H. Comroe, Jr.)

body size,[113] but appears to be related to rate of metabolism. For example, (See Table 11) the mouse has the smallest alveoli mean diameter, the guinea pig and rat almost two times that of the mouse and the cat and man approximately three times the mouse. From such data, Tenny[113] attempted to relate pulmonary ventilation to easily measured physiological and physical measurements. He determined that total alveolar ventilation is proportional to metabolic rate of the species; respiratory frequency correlates inversely with body mass to the 0.28 power; metabolic rate correlates with body weight to the 0.74 power; total lung volume is a constant fraction of body mass and tidal volume is directly proportional to body weight.

4. Mechanics of Breathing

Air flows from a region of higher pressure to one of lower pressure. Respiratory movements, reflex or not, determine the degree and extent of pulmonary pressures through voluntary and involuntary muscular control. Active contraction of the inspiratory muscles causes enlargement of the thorax and lowers the intrathoracic pressure, thereby enlarging the alveoli, expanding the alveolar gas, and lowering the overall alveolar gas pressure to less than atmospheric so that air flows into the alveoli. Active muscular contraction during inspiration provides:[22]

a. The force necessary to overcome elastic recoil of the lungs and thorax.

b. The force required to overcome frictional resistance during movement of the lung and thoracic tissues.

c. The force necessary to overcome frictional resistance to air flow through the tracheobronchial tree.

At end-inspiration, the muscles of inspiration relax and no longer exert a force which distends the lungs and thorax, the

elastic tissues of the lung and thorax now recoil. In normal subjects the elastic recoil results in the lungs and thorax returning very rapidly to the resting expiratory level even though expiration is completely passive.

There are species differences in the breathing mechanisms as one would expect. The eupneic horse moves approximately 6000 ml of air over a span of five seconds.[84] The respiratory cycle is polyphasic with dual expiratory and inspiratory phases. The thoracic movement is usually less than the abdominal. The dual cycle normally becomes obscure in abdominal movements during hyperpnea, but persists in increased respiratory (nasal and trachea) and intrapleural inspiratory pressures. In the dog, the intercostal muscles and the diaphragm do not act together in inspiration with respect to time. The early air flow peak that is observed in inspiration is due to the action of the intercostals, and the late peak flow is due to the action of the diaphragm.[124] In the eupneic rat, the respiratory cycle moves 1.5 ml of air per second. The cycle is diphasic with single expiratory and inspiratory phases.[84]

The elastic properties of the lung and thoracic tissues are combined into a parameter called pulmonary compliance which is defined as the volume change per unit pressure change and is expressed in units of liters/cm H_2O. Pulmonary compliance is measured under static conditions. When elastic properties are measured under dynamic pressure-flow relationships, they are referred to as pulmonary resistance and are defined as pressure differential required for unit flow change and are expressed in units of cm H_2O/liter/sec.

Lungs of small and large animals tend to have approximately equal pulmonary compliance thereby requiring approximately equal thoracic pressures for intake of one tidal volume.[38] Pulmonary compliance differences nevertheless exist and are tabulated for the various species in Table 12. It is apparent by examination of Table 12 that species differences are observed in other respiratory parameters such as tidal volume and frequency of breathing.

Agostoni and co-workers[1] reported that the expiratory reserve per unit vital capacity and the functional residual capacity per unit total lung capacity are larger in the animals breathing at a lower frequency. The relationship between rate of work of breathing and breathing frequency was such that the frequency typical of each animal at rest corresponded to the minimum rate of work. This increased frequency and its effect on alveolar pO_2 is possibly the primary factor concerned in species differences.[109] The panting mechanism supports this view, as respiratory impedance is least at the resonant frequency of the thoracic system, and volume flow is obtained with least effort at this frequency.[27] McCutcheon[83] described a complementary cycle in the horse and rat. He defined the cycle as a predictable recurrence in regular sequence. This cycle is a very deep, rapid inspiratory movement (initial rapid respiratory movement) followed by a very slow expiratory movement. The complementary cycle frequency was found to vary with body size but the duration of the cycle varied more with the alveolar size than with body size. (See Tables 10 and 11). He suggested that diffusion regulation in respiration is a principle of the comparative physiology of atmospheric respiration of various species and that

periodic breathing is the primitive pattern of atmospheric ventilation. Other factors influencing the pulmonary ventilation and, therefore, deposition are:

a. Protective reflexes:

(1) Cough reflex - produced by forceful expiratory effort generated as a response to foreign materials or secretions introduced into the respiratory tract.

(2) Upper respiratory reflex - causes apnea, closure of the glottis and bronchial constriction when irritating materials enter the upper airway.

(3) Swallowing reflex - food passes from the mouth to the esophagus by closure of the glottis and inhibition of inspiration.

(4) Submersion reflex - causes apnea and bradycardia when water enters the upper respiratory tract.

b. Pulmonary stretch reflexes:

(1) Hering-Breuer inflation reflex - inhibition of inspiration in response to lung inflation. It has been seen in such animals as man, dog, cat, monkey, rabbit, guinea pig, rat and mouse.[119] The inhibition period in man is 2 to 20 times shorter than the rabbit.

(2) Hering-Breuer deflation reflex - deflation or collapse of portions of the lungs causes earlier and more rapid inspiration and acceleration of respiratory frequency. The reflex is weak in humans, but strong in many other animals.[119]

(3) Head's paradoxical reflex - this has been observed in cats, dogs, monkeys and rats, but never in man.[119]

c. Thoracic chemoreflexes: (Bezold-Jarisch reflexes)

Stimulation of coronary and pulmonary chemoreflexes results in reflex apnea, bradycardia and hypotension via vagal stimulation. Effects may be dramatic and sometimes catastrophic in experimental animals,[22] but effects vary in different species and the physiologic or pathologic significance of these reflex effects in man is still obscure.

d. Circulatory factors:

(1) Increase in arterial blood pressure in the carotid sinus and aortic arch reflexly diminishes pulmonary ventilation, and a decrease in arterial blood pressure augments the pulmonary ventilation.

(2) Severe hypotension may cause ischemia in the carotid and aortic bodies resulting in an intense respiratory stimulation.

(3) An increase or a decrease in cerebral blood flow may decrease or increase pulmonary ventilation respectively by permitting a change in CO_2 content of neurons in the respiratory center.

e. Reflexes from joints:

Back and forth motion of a limb will reflexly increase the rate and occasionally the depth of breathing.

f. Pain receptors:

Respiratory stimulation or inhibition may be caused by pain depending on the character, origin and intensity.

g. Temperature:

An increase in body temperature will cause an increase in pulmonary ventilation. This results, in part, from "warming" of the medullary centers and chemoreceptors.

h. Supramedullary regulation:

Supramedullary areas exert important effects on areas such as pontine, pneumotaxic center and cortical areas.

Pathological or physiological alterations in the respiratory tract will considerably modify the air flow and, therefore, the amount of alveolar ventilation; the latter indirectly affects the deposition and the distribution of material in the bronchials and pulmonary lobules. For example, the different air velocities and alveolar ventilation rates in a fast shallow breather versus a slow deep breather in the human may be compared to a panting

dog with dyspnea or to a horse with emphysema. The variation in ventilation rates will cause differences in the total amount of material deposited and probably differences in the distribution to the specific areas of the respiratory tract.[90] The distribution of air to the normal lung lobes is not necessarily in proportion to their volumes nor does each lung lobe become ventilated equally. Rahn et al,[100] by perfusion of canine lung with radioactive materials following autopsy, observed unequal ventilation of the lung in the supine and erect positions.

The typical radioactive field aerosol is heterogenous in that it contains a large fraction of small particles of relatively high radioactivity, such that the contribution of these particles to the radiation dose, despite relatively low deposition, may produce a major fraction of the total dose. A point to remember is that physiological parameters, such as breathing frequency, can exert about as much influence as particle size. It has been shown numerous times that the fast shallow breather will have relatively less material deposited in the lungs than the slow deeper breather when all other factors are equal. This same effect has been seen by investigators for the sub-micronic range of particle sizes.[42]

It is quite evident that there are many physiological and physical factors involved in the study of total lung volumes. Neither metabolic rate nor surface area directly affects this volume; however, total lung volume appears to be a constant fraction of body mass in that tidal volume is directly proportional to body weight and a constant fraction of the lung volume.[113]

Some of the physiological factors which may determine the gas flow into the tracheo-bronchial tree have been discussed with emphasis on particulate deposition and interspecies differences. Before discussing work done in radioiodine inhalation a brief discussion of a lung model is in order.

5. Lung Model

The lung model to be discussed here assumes some form of an airflow (velocity versus time) pattern in the airways and still air in the alveoli. Silverman[105] stated:

> "In many instances these model assumptions can be improved by adaptations of actual air flow data. The important consideration is that air flow varies throughout the whole respiratory cycle, except for a short pause following expiration under sedentary conditions only. This would indicate that inertial mechanisms of removal in the nasal passages and in the upper respiratory tract and at bifurcations, etc., must be essentially a function of a variable velocity, a consideration that requires an extension of the existing theories for inertial deposition."

The model does not consider pulsations of gas flow within the lung which are caused by movement of the heart or great vessels, West[117] stated:

> "The observations of pulsatile flow will affect any theory of dust deposition which is based on the assumption of still air in the smaller airways."

However, the proposed lung model is used for calculation of deposition and clearance information and for determining maximal permissible air levels of gases, vapors or particulate matter. Hursh[68] stated:

> "The lack of element specific information and the excuse of long practice have justified the use of this convenient device."

This model predicts that 75% of the total radioactive particulates inspired will be deposited, 25% will be expired. Of the 75% deposited, 50% will be deposited in the upper respiratory tract and the remaining 25% in the pulmonary lobules. It distinguishes between the behavior of soluble and insoluble classes of inhaled materials in the pulmonary lobules. In the case of soluble materials, the 25% passes rapidly into the blood; in the case of insoluble materials 12.5% is removed by the pulmonary system and ends up in the gut; the other 12.5% is slowly removed from the lung by absorption in blood and lymph with a half-life period of 120 days (See Table 13). Gibb[54] reported approximately 12% alveolar deposition in the dog of an insoluble ^{59}Fe oxide aerosol with a biological half-life for alveolar clearance of 62 ± 8.8 days. These amounts of deposition were highly reproducible; however, this is not always true for man because total lung deposition of dusts has been observed to vary from 20 to 90%.[91]

It should be noted that there is marked evidence that any pulmonary study will show conspicuous species differences not usually considered in the lung model. These differences become more acute as the methods of study begin to obtain refinement and calculations of radiation dose become more critical.

C. RETENTION AND CLEARANCE

Retention is defined as the amount or fraction of deposited material that remains in the respiratory tract at any given time. Retention is expressed as the percent of the total radioactive aerosol inhaled which remains deposited in the lungs. The transport of the deposited material out of the respiratory tract is referred to as

clearance. As the material is being deposited, pulmonary clearance mechanisms are normally functioning to remove the material; therefore, deposition, retention and clearance, when measured as such, vary as a function of time. The end result is removal of material from the respiratory tract. The four physiological mechanisms involved in the transport of the particulate material from the lungs are 1) action of the ciliated bronchial epithelium, 2) alveolar phagocytosis, 3) transfer of relatively soluble material across the alveolar membrane, and 4) penetration of the alveolar wall without mediation of phagocytic cells.

1. Physiological Mechanisms of Pulmonary Clearance

   a. Ciliary Clearance

      The ciliated epithelial lining of the bronchial tree plays a major role in the clearance mechanism of the lung. Mucosa which comes into contact with the majority of inhaled impurities is located in the nostrils, trachea and larger bronchi. The degree of contact with the finer bronchi and bronchioles is, for the most part, dependent on deposition mechanics and absorption higher up in the bronchial tree.[30] Regardless of how particles are brought in contact with the ciliated epithelium, the particles normally never contact the cilia directly, but lie on and/or in a blanket of very thick and viscous mucus which overlays the cilia of the bronchial epithelial cells.[77] The mucus and the embedded particles are driven upwards "in bloc" by the rhythmic beating of the cilia. The cilia have been reported to average 1099 beats per minute in the rabbit.[30] The cilia force the mucus upward along the bronchial tree in a spiral path to the pharynx where it is eliminated either by coughing or by

swallowing.[77] In rats, radioactive particles have been shown to be cleared from the ciliary lined air passages within one day.[103] The linear velocity of particles moving up the bronchi varies from 0.25 to 1 centimeter per minute and increases to as high as 3 centimeters per minute in the trachea.[11,42,46] The process by which particles are carried up the surface of the bronchus toward the pharynx is referred to as a "mucus-cilia escalator".

b. Alveolar Phagocytosis

Clearance of the pulmonary tract of matter, foreign or secretive, involves a second mechanism referred to as alveolar phagocytosis. Inhalation of particulate matter causes the appearance of a large number of amoeboid cells that apparently have a dual capacity to act as macrophages or to remain free in the alveolar lumen. These cells, referred to by many as pneumocytes, may phagocytize inert dusts in large quantities and undergo mitosis or may engulf toxic dusts and then undergo degenerative changes.[102] Schiller[102] distinguishes between two types of pulmonary phagocytes. The first type is the cell derived from the alveolar epithelial cells. These cells are on the alveolar surface and do not enter the interstitial tissue, but are removed with the pulmonary fluids. The second type is a cell derived from the interstitium and is considered to be sub-epithelial in origin. These are found most generally in the interstitial connective tissue of the lung. He concluded that there are two phases of phagocytosis, the epithelial phase of phagocytosis by pneumocytes and the interstitial phase of phagocytosis by macrocytes. Casarett's[19] theory differs

somewhat in that the origin of the phagocyte is apparently the alveolar epithelial cell. The phagocytic ability of the cell is considered to be the manner in which the cell membrane is arranged with regard to the adjacent cell; i.e., one cellular membrane may be on the lumen side of the alveolar segment whereas the cellular membrane below it is on the interstitial side of the segment. He, therefore, is of the opinion that the particle-laden phagocytes that appear in the alveolar lumen are those cells that have full cellular exposure to the lumen; those particle-laden phagocytes found in the interstitium are those cells that have cellular exposure to the interstitium. He also feels that particles can penetrate the alveolar wall directly without benefit of phagocytic transportation.

The rate of phagocytosis has been found to be a function of the particle size,[42] particle concentration,[77] physicochemical properties of the particulate matter,[61] and surface tension of pulmonary fluids.[96] It appears that the process would continually progress, regardless of rate, as long as there were potential histiocytic cells to respond to the irritation of foreign matter. If the alveolar cells were destroyed or the cells became amitotic for one reason or another, phagocytic activity would cease and alveolar fibrosis would normally occur.

La Belle,[77] by estimating the number of free phagocytic cells in the lungs of rats, concluded that transport of deposited particles by phagocytes was the primary mechanism by which inhaled insoluble dust particles were eliminated from the lung following inhalation. He showed that the amount of

dust eliminated from the lung during the early post-exposure period was proportional to the number of free phagocytic cells present and that the kinetics of elimination of the particles was identical with the kinetics of the disappearance of phagocytic cells following exposure to dust, whether the dust was given by inhalation or by injection.

c. Alveolar Membrane Transfer

Transfer of relatively soluble material across the alveolar membrane into the blood stream is the third mechanism of respiratory tract clearance. The terms "soluble" and "insoluble" are placed in quotes since solubility is dependent principally on chemical composition; however, physical properties such as size, shape and surface area are also involved. Simple solubility in pure solutes need not be a measure of solubility in the lung.[42] For example, $Ag^{131}I$, a most water-insoluble iodine compound, once inhaled does not act as a purely insoluble compound.[120,121] The assumption that material leaving the lung passed into the systemic circulation via the blood vascular system if the particle were soluble, and via the lymphatics if it were insoluble, was made before actual experimentation was attempted. Balance sheets for pulmonary deposition, retention, and transport have been proposed in an attempt to explain the clearance of the lung. Numerous calculations and observations indicate that a satisfactory explanation of the observed dynamics of the lung itself has not yet been obtained.[77]

Harper and Morton[61] demonstrated that inhaled ^{32}P tagged aggregates of bacterial spores were eliminated via

the gastrointestinal tract. This apparently was the earliest experimental demonstration of clearance of inhaled, insoluble particles from the lung via the "mucus-cilia escalator" into the gastroenteric tract. This clearance was chiefly from the upper respiratory tract where total percentage retention of spores is known to decrease.[15] The remaining particles may or may not have contained radioactive material that could cross the alveolar membrane. If gaseous and particulate matter are inhaled, such as often happens with radioiodines or compounds that sublime easily, the transport of these compounds through the lining complex of the alveoli is dependent, for the most part, on physicochemical interactions of the inhaled matter with body components.

Pattle[96] described the lining of the alveoli as an insolbule layer formed from a thicker layer of a substance which he called the "lining complex". This layer was found capable of reducing the surface tension of the alveolar surface to nearly zero while being fully permeable to air (and presumably to any vapors). He was of the opinion that it is possible that the lining complex responds to inhaled irritants by an increase in secretion, thereby lowering the surface tension and providing a protective mechanism for the alveoli.

It is apparent that more than solubility is involved in clearance of material from the lung, since it has been demonstrated that translocation is not necessarily predictable from the solubility of compounds in pure substances.[8,77] Vapor pressure is possibly a more important limiting factor than water solubility during short term experiments.[2]

d. Non-Phagocytic Penetration of Alveolar Wall

The fourth mechanism involved in lung clearance is the penetration of the alveolar wall without mediation of phagocytic cells.[6,19,33,42,102] This mechanism affects particulate matter which has been deposited in the deeper portions of the respiratory tract where, for the most part, clearance by the "mucus-cilia escalator" has been ineffective, non-functional or non-existent; however, the existence of this mechanism has not been fully proven.[42] The penetration of the lining complex of the alveolus is thought to take place at multiple, small, scattered foci near the juxtaposition of alveoli and large vessels and bronchi.[42] Others have suggested that the penetration of the alveolar lining membrane occurs through defects in the membrane.[33] Schiller[102] maintains that only free particles can penetrate the walls of the alveoli and that a pneumocyte or phagocyte laden with dust either stays in the lumen of the alveolus or is transferred to the bronchioles and expectorated. If destruction of a phagocyte occurs, the process of clearance is repeated. Barclay[11] discussed the mechanism by which phagocytes cross the continuous cytoplasmic structures and vital membranes. The mechanism is unknown and probably related to diapedesis.

Discussion of the mechanisms of lung clearance have purposely omitted the nose, sinuses and extreme upper respiratory tract. Clearance mechanisms of this portion of the respiratory tract are similar; however, removal rates are more rapid, probably because the majority of this portion of the respiratory tract is lined with ciliated epithelium.

Over 90% of a very soluble gas such as Sarin was found to be absorbed in the nasal cavity; however, the nose would not protect the lungs during a prolonged exposure to the gas.[2] Pattle[95] also found that after prolonged exposure to a noxious soluble gas, the nasal mucosa would reach a balance between the absorption of the gas and its diffusion into the blood stream. Retention in the nose was nearly 100% for particles above 9 microns in diameter and variable between 1 and 9 microns. Penetrations posterior to the trachea and below were 90% at particle sizes of 1 micron in diameter. The variation in retention suggests that impaction is the main mechanism by which these particles are retained. Particles measuring 0.054 to 0.4 micron in diameter showed penetrations averaging 80%; no regular variation with flow rate or particle size could be detected. West[118] found that the upper respiratory tract removed water vapor with a high degree of efficiency. He scanned the respiratory tract of three human subjects immediately after they had inhaled ^{15}O labeled water vapor. It was found that the mouth, pharynx and upper trachea retained a large percentage of the ^{15}O water vapor (See Table 14). Barrall[12] compared the radioactivity on nose swabs to resulting thyroid burden in a patient accidently exposed during a contamination incident. He found the ratio of microcuries on the nose swabs to microcuries in the thyroid was 2.6×10^2 with all values within a factor of six.

D. TRANSLOCATION

Translocation is defined as the movement of material from one tissue to any other tissue or tissues. Translocation takes place to a certain extent irrespective of the physico-chemical nature of the inhaled radioactive material. This leads not only to a direct radiation hazard to the lung, in the case of inhaled material, but also to a systemic radiation hazard by virtue of absorption and deposition in other tissues.

During clearance of radioiodines from the lungs, the radioiodine may enter the systemic circulation via such routes as the pulmonary or the gastroenteric complex. The distribution of radioiodine in tissues following lung clearance, is qualitatively similar to the distribution in tissues following intravenous administration.[41] Certain radioiodine compounds may be exceptions to this under special conditions. Pulmonary clearance was apparently very rapid in mice following inhalation of ^{131}I vapor.[7,9,119,121] The maximum concentration of ^{131}I was shown to appear in the thyroid at about 30 hours. There was a simultaneous decrease of ^{131}I in the lung and other tissues. This was probably a reflection of the ^{131}I uptake of the circulating blood. Under similar experimental conditions, but substituting a relatively insoluble Ag ^{131}I compound for the carrier free ^{131}I, mice were found to retain 12% of the Ag ^{131}I; however, the time of maximum thyroid uptake was 10 hours. A finding such as this could be regarded as an exception to the statement made previously. Nevertheless, it still may be true that the blood and lungs, with respect to inhaled iodine, will rapidly enter into iodine equilibrium. Sheep and rats were found to be qualitatively similar in deposition, retention and thyroid translocation, although quantitative results did not completely agree.[13,121] Fountain[48] showed the thyroid uptake

following cloud passage from Project Sedan was 92% of the total ^{133}I available to the respiratory tract of Beagles. It is highly probable that the dogs licked themselves following exposure to the cloud and therefore one cannot assume that the entire intake of radioiodine was by inhalation.

The concentration of radioiodines in the systemic circulation may be due to a large percentage of the deposited particulate matter containing the radioiodines being eliminated from the lung via the "mucus-cilia escalator" and then being coughed up, swallowed and absorbed via the gastroenteric route. It has been suggested that the gastrointestinal tract can be an important route of entry of inhaled material into the systemic circulation.[42] If this is true, evaluation of the internal hazard associated with radioiodines, either in soluble or insoluble forms, requires further investigation and consideration of parameters that influence transport of radioiodines across the gastrointestinal membrane.

Regardless of how radioiodine enters the systemic circulation, a large percentage of the iodine is usually translocated to the thyroid under normal physiological conditions. The thyroid, therefore, is assumed to be the critical organ with regard to internal radiation hazards from radioiodine.

1. Fate of Radioiodines in Body

The thyroid consists of two lobes, one on each side of the trachea, and, in the horse, cow, sheep or dog, a very narrow connecting isthmus near to or in contact with the larynx. In the dog the isthmus usually disappears in embryonic life.[39] In the pig, the glands are usually found a distance from the larynx and are united to a considerable extent ventrally by an isthmus which

cannot be distinguished.[106] The gland is composed of numerous follicles that are lined by a single layer of low cuboidal epithelial cells which contain colloid. There are species differences in size and weight of the gland as well as differences in volume of air breathed per gram of thyroid and weight of thyroid per kilogram of body weight. Dairy cattle breathe approximately two liters of air per gram of thyroid per minute, but in contrast, man breathes only 0.2 liters of air per gram of thyroid per minute[115] (See Tables 12 and 15).

Grazing type animals breathe a large quantity of air and also ingest large amounts of food per gram of thyroid. Van Middlesworth[115] was of the opinion that these characteristics explain the reason why thyroids are early indicators of radioiodine in the biosphere. He suggested that the lowest retentions of radioiodine fallout may represent only the respiratory intake. Another factor that should be considered is the physiology of the mechanism of eructation in the ruminant. Dougherty et al[36] reported that the pulmonary system provides a route of absorption of eructated gas. They found that various gases such as CO_2, CO, H_2S, and O_2 (and no doubt radioactive iodine vapor if it were present) after being placed in the rumen were more capable of causing changes either in the blood gas levels or in physiological activities of the animal when the trachea was patent and capable of receiving these gases during eructation. Dennis and Harbaugh[34] found that average blood CO_2 for the Jersey was 53.6 volumes percent and for the Holstein (a big breed of cow) was 56.5 volumes percent. These percentages varied inversely with the ambient temperature of their environment.

Following absorption into the blood vascular system the majority of iodine appears as an organic iodide which diffuses rapidly into the extracellular space[24] or is oxidized and incorporated into organic compounds, usually proteins.[115] The first mechanism is referred to as the extrathyroidal iodine pump. This mechanism transfers iodide ions from the plasma into other pools where the I^- concentration is maintained 10 to 40 times greater than in plasma. Apparently, the salivary duct and gland, gastric mucosa, and skin concentrate iodide ions in much the same manner as the thyroid gland. Salivary glands and gastric juice have been found to contain iodine 30 and 40 times greater than plasma, respectively.[24] Iodides are normally freely exchangeable with plasma in the skin, cerebrospinal fluid and placenta.[24,115] Concentrations of ^{131}I in the fetal thyroid during advanced gestation may be 1 to 2 times the adult thyroid in sows, 2 to 3 times the thyroid in ewes, and up to 6 times the thyroid in cows.[31]

Blood iodine will directly influence the thyroid function if it is readily available as an iodide ion. However, variations are also associated with age, breed and season in some animals.[123] In sheep the maximum thyroid uptake was found to be during the period from August to January and the minimum uptake from April to July.[17] A suggestion of increased thyroid uptake has occurred following parturition in the dairy cow.[18] Swanson et al[110] reported the maximum accumulation of ^{131}I in the thyroid of the dairy cow was about two times as great in November as May, about the same in September as in May and lowest in July. The extrathyroidal iodide pools may function as buffers and act as a control system to aid in the maintenance of a constant

mass of iodine transferred into the thyroid per day. The quantity of iodine, whether radioactive or stable (^{127}I), accumulated each day by the thyroid gland is characteristic of the species and is the fraction of the daily iodine intake and extrathyroidal iodine pool which is trapped by the thyroid gland. Rapid accumulation of iodine by the thyroid may indicate inefficient utilization of iodine[115] and pathological alterations.

The thyroid gland removes iodide from the plasma through the thyroidal trap, which depends on intact follicular cells and possibly a binding on a special protein.[24] The trapping does not apparently depend on specific metabolic pathways for iodide because these can be blocked by antithyroid drugs without abolishing the concentrating activity. Recycling was found to be prevented in dairy heifers by giving thiouracil at the rate of 0.2 grams per kilogram of body weight, but not by giving subcutaneous KI.[80] Bair and co-workers[9] found that to reduce the ^{131}I uptake 50 - 100 fold in rats and 3 fold in dogs, it required a concentration of iodine (^{127}I) aerosol that acted as an irritant to the respiratory tract. Thus it appeared that a near toxic level of ^{127}I in air was required to significantly depress the thyroidal uptake of ^{131}I under the condition of the experiments. The mechanisms that are involved deal with metabolic pathways which are not easily traced and are concerned with many interactions of various hormones. Recent advances in iodine metabolism and the biochemistry of hormones are well documented in published references.[28,87,99,116] These references should be consulted for greater detail.

Comparisons between various methods of administration of the radioiodines contributing to the iodine pool show variations

in percentage of uptake by the thyroid. A single dose of Na ^{131}I injected subcutaneously in 63 dairy heifers of four different breeds resulted in a maximum thyroid uptake in 48 hours[80] (See Table 16). The thyroid was found to contain 41.6% of the injected dose. Wood and co-workers[123] reported that rates, total uptake and effective half-life were similar in young sheep following oral, intravenous and subcutaneous administrations of ^{125}I and ^{131}I. A lower uptake and a longer effective half-life were seen following topical administration of both isotopes. There are found in the literature conspicuous differences in absorption rates of various radioiodine compounds given by various methods (See Table 17). The absorption from the different sites emphasizes the unusual properties of body fluids and shows that one cannot always predict the absorption of ^{131}I from the body tissues on the basis of solubility of the compound.[121]

2. Excretion of Radioiodines into the Mammary Glands

Iodide loss by excretion is predominantly through the mammary gland, hair and perspiration. Iodine is concentrated in the hair, but the biological importance of this fact is a relatively unexplored field.[115] The sweating mechanism is markedly different between species. Man has the most refined mechanism whereas the dog has relatively few sweat glands. In domestic animals, especially dairy cows, a major portion of the iodide loss is through the mammary gland. Available iodide passes to and from the mammary gland and blood with ease, entering the milk independent of milk secretion.[89] The iodide or iodine enters the udder of the cow passively, but once in the milk collecting spaces, a portion of the iodine is bound and is rendered non-available for resorption. The greater iodine excretion of

higher yielding cows is no doubt related primarily to increased mammary circulation and therefore to their greater volume of milk. The milk seldom contains more than two times the plasma concentration of iodide. The protein-bound iodine is between 30 to 50% of the total iodine.[115] However, this does not appear to be true in the goat and sheep. The milk from either of these species has been found to contain 10 times the iodine concentration normally appearing in cow's milk. Garner et al[51] demonstrated the presence of a concentrating mechanism in the udder of the dairy cow. The comparison of the total ^{131}I in milk to plasma dialyzable ^{131}I at different times of the year indicated that the concentrating ability may be lower in the summer than in the autumn and spring months.

Excretion, if the reader will accept this term, of ^{131}I into the mammary gland per liter of milk has been determined to be approximately 0.4 to 1% of the daily ^{131}I intake after reaching equilibrium;[18] however, a marked variation is encountered among individual cows and among herds. Garner et al[51] showed a total recovery of ^{131}I in milk during a 6-day collection period as 1.3 to 19.4% of the initial dose. Other authors have shown recovery of $6.2 \pm 2.0\%$ of the dose during a period of seven days.[24] Bustad et al,[18] after spiking forage with 5 microcuries of ^{131}I and feeding this twice daily found that on the fourth day, 0.4% of the first day's dose of 10 microcuries was observed per liter of milk. Peak concentration of the thyroid was seven days and was about 70% of the first day's dose. Swanson et al[111] demonstrated that 7.2% of the initial intravenous dose of Na ^{131}I was recovered from the milk by the third day post-injection. Squire et al[108] reported that there appeared to be no evidence of any

difference between the total excretion from cows fed fission products serially or on a single occasion. The fission products, which were collected on gauze-backed, oil impregnated filters following round 1 and round 3 of Operation Buffalo, contained ^{131}I, ^{132}I, ^{132}Te, ^{133}I and other radionuclides. The material on the filters was considered comparable to long range fallout. They found that 1.48% and 3.48% of the administered dose was recovered during a nine day and six day period, respectively. The concentration in milk of ^{132}I was at least twice as high as ^{131}I in the early stages. Iodine-132 declined to 50% at the end of six days. Iodine-133 decayed to an insignificant amount after eight days.

3. Excretion of Radioiodines into the Feces and Urine

Fortunately, the largest quantity of iodine is lost through excretion into the feces and urine (See Table 18). Fecal loss of iodine is apparently a major route of depletion in rats, cattle and sheep because these animals not only have large daily requirements of thyroid hormone, but also excrete large quantities of organic iodine in the feces.[115] Swine and man are more conservative with their iodine reserves for only a small fraction of thyroxin that enters the gastrointestinal tract is excreted in the feces.[17,24] The major difference appears to be the fecal:urine ratio in the various species. The factors involved in the excretion of thyroxin into the feces are unknown.

Renal clearance of iodine in euthyroid humans is a linear function of the glomerular filtration rate and appears to be primarily an overflow mechanism for iodide.[24, 115] Rats will excrete more iodide if given Na Cl whereas the human is not

affected by electrolytic changes as such. Taplin and co-workers[112] suggested that ^{133}I could have been inhaled by rabbits following a tower detonation. Urine was found to be suspicious at 55 and 117 hours post-exposure, but they could not establish this with any certainty. Barry[13] reported that a 24-hour urine sample collected from rats that had inhaled ^{131}I contained over 50% of the estimated inhaled dose. Bair et al[9] reported that 96% of the excreted ^{131}I was in the urine of rats exposed to ^{131}I-^{127}I aerosol. Monogastric animals have been found to excrete more ^{131}I in the urine than in the feces.[31] Barrall[12] demonstrated that in man the ratio of microcuries in a 24-hour urine sample to the microcuries of ^{131}I in the thyroid was 5..7 with all values within a factor of two.

Radioactive iodines that are not translocated to the thyroid, secreted or excreted are found in various organs. Less than 1% of an oral dose of ^{131}I was found in body organs other than the thyroid of patients either at autopsy or surgery.[76] Organs of uptake in descending order were lung, kidney, pituitary, liver, gonad (testes were always measurable), spleen, adrenal and pancreas. In rats,[7,121] following inhalation of ^{131}I or Ag ^{131}I, the gastrointestinal tract, liver, lung, kidney, spleen and thyroid were found to contain measurable amounts of radioactivity (See Table 19). This was considered as a reflection of iodine equilibrium beginning to establish itself in the plasma. By 50 hours the thyroid had received 60% of the total body burden. Bustad et al[17] listed the tissues containing ^{131}I following establishment of ^{131}I equilibrium in the blood of the sheep; the thyroid, feces, mandibular salivary gland, milk, abomasal wall and urine contained concentrations of ^{131}I higher than those

found in the blood. Other tissues, listed in descending order, that contained concentrations of ^{131}I less than the blood were the parotid gland, liver, ovary, kidney, adrenal, pituitary, lung, lacrimal gland, heart, pancreas, spleen, thymus, brain and lens.

Although the thyroid apparently receives the greatest percentage of body burden following exposure to radioiodine, other organs and tissues are also exposed at some time during the circulatory and/or storage phase. The rates of exposure depend on many factors such as solubility, route of administration, species, etc.; however, the rate of translocation, for the most part, depends on the concentration of ^{131}I in blood and the integrity of the blood-vascular system to the various organs and tissues. When the blood concentration of ^{131}I is 1 picocurie per gram of blood, the following relations exist in the tissues of the sheep and supposedly other ruminants.[31]

Tissue	Blood Concentration of ^{131}I in Picocuries per Gram
Muscle, spleen, thymus, pancreas	1
Kidney, liver, ovary	2-3
Salivary glands, urine	3-5
Feces, milk	5-15
Thyroid	10,000

The obvious factor is that the thyroid receives by far the greatest fraction of the total body burden. The radiation dose to the thyroid gland from a chronic exposure to radioiodines would be a function of the total deposited radioisotope in the gland. In a single exposure the radiation dose would be determined by the rate of thyroid uptake and be related to the biological half-life. Species characteristics will, however, determine the

radiation dose to that particular species since there is a variation in biological half-life of iodine in each (See Table 15). Not taken into consideration are the seasonal fluctuations that occur as well as pregnancy, lactation, temperature and possibly photoperiodicity.[17,115]

Irrespective of how the individual (man or beast) is exposed to radioiodines, the end result has been assumed to be thyroid damage. The degree of damage apparently depends on species, although rate of uptake and iodine in the diet have to be considered as well. In the cow the minimum radiation dose to the thyroid required to produce a deleterious effect on the animal was estimated to be of the order of 70,000[31] to 100,000 rad.[53] Wood et al[123] estimated the total radiation dose to the sheep thyroid from oral administration was 6 to 8 rad per microcurie and from topical administration was 2 to 3 rad per microcurie..

Review of the comparative pathology following exposure to radioiodines suggests that there is morphological evidence of inflammation and necrosis in the thyroid.[52] An apparent sequence of morphological alterations appears to occur more rapidly in rats and mice than in dogs, and even more slowly in human beings.[79] Definitive pathological findings in the human are still in question in the greater percentage of cases. These findings on pathological effects from thyroid irradiation were summarized and reported by a panel of experts in 1962.[94] Their findings were:

a. Differences in size and proportion of proliferating cells of the thyroid in infants, children, and adults do exist.

b. There may be significant alterations in absorption, metabolic turnover and cell sensitivity with advancing age.

c. Any of the above factors might affect the amount of biological damage resulting from a given radiation dose.

d. At high dose levels, the thyroids of infants and children may be somewhat more susceptible to radiation carcinogenesis than those of adults.

e. Evidence of carcinogenesis at very low doses is lacking because no case of thyroid cancer at these levels is known.

f. Radioactive iodine has been shown to be carcinogenic in some animals, but no case of thyroid cancer ascribable to it has been found in man.

V. SUMMARY

Quantities of radioiodines released into the biosphere are dependent on the characteristics of the source of fission products. However, after being released, atmospheric, terrestrial and aquatic influences will normally determine the transport and the ultimate deposition. Following release into the biosphere, the transport and diffusion of radioiodines are usually considered to be uniform for the same release and meteorological conditions since the physico-chemical nature of the contaminant depends on the nature of the total release conditions. The biological availability will, therefore, depend a great deal on such physical factors as the source of radioiodines, proximity of the source to biological systems of interest, and meteorological conditions existing pre- and post-release. The problem, however, is the prediction of the many different chemical forms as well as physical forms the radioiodines may assume. They may be adsorbed in or on particulate matter, may exist as gases or vapors, or may be present in combinations of all three. The iodines may be found as elemental iodine, iodide (I^-), iodate (IO_3^-) and periodate (IO_4^-) or as organic compounds. The chemical states, solubility and physical states of the radioiodines greatly influence their behavior and in turn their possible absorption in a biological system and their availability to the respiratory system. The size of the particle upon which the radioiodines are absorbed or adsorbed depends in part on the origin of the particulate matter. The availability of the particulate matter to the respiratory tract will depend on whether the MMD of the particles is within the respirable range, i.e., a significant number of particles below approximately 10 microns in diameter. The region of deposition will depend upon such parameters as the particulate size,

oral or nasal inhalation, flow rates through the respiratory dead space, and the alveolar ventilation.

Rate of deposition of particles within the respirable range in the lung is dependent, for the most part, on the physiological characteristics of the pulmonary system of the species. There is a conspicuous difference in oral or nasal breathing among the various species. . . Man as a rule is a nasal breather; horses usually breathe through the nose as do cows and sheep; dogs use oral and nasal breathing interchangeably depending on body temperature regulation, and cats are similar to dogs except they normally pant less. Flow rates through the airways depend, in part, on the diameter of these passages, their length and the degree of "straightness". The volume of alveolar ventilation is dependent on frequency of breathing, tidal volume and amount of respiratory dead space. These three factors will determine the total and effective ventilation of the lungs and indirectly determine the amount of deposition of "respirable" particles. Quantity of total ventilation, however, is characteristic of the physiological and anatomical features of the species. Each species differs in metabolic rates, respiratory frequencies, body mass, and total lung volume. Each of these has an effect on the total alveolar ventilation. In addition, there are species differences in the mechanics of breathing. The horse has a diphasic breathing pattern with no complementary cycles and the rat has monophasic pattern with many complementary cycles. Man and domestic animals exhibit patterns between these two extremes.

Retention and clearance are usually considered under the same discussion since they are inversely proportional to each other and are treated as rate functions. The removal of foreign matter from the lungs is by four physiological mechanisms peculiar to the lung. These mechanisms are found to be functional in all species of mammals, but

differ in the degree to which they participate to clear the lung of foreign matter.

As retention and clearance are taking place, translocation (the movement of material from one tissue to any other tissue or tissues), is usually being accomplished. This takes place, to a certain extent, regardless of the physico-chemical nature of the inhaled radioactive material. Translocation of the radioiodines is predominantly to the thyroid irrespective of the route of entry into the body.

Since the most common route of entry of the radioiodines has been assumed to be by ingestion, past interest has been in ingestion with very little, if any, regard for inhalation. This is not surprising since investigative programs to study inhalation of radioiodines are not easily done, especially in large animals such as the milk cow. The contribution of the radioiodines to total body burden following inhalation by dairy cows in the field and excreted into the milk has not been investigated in detail. The excretion of the iodines into milk and uptakes by thyroids of sheep and cows from other routes of entry are well documented; however, individual variances appear to be the rule. Time of year, pregnancy, age, breed, production, and diet, to mention a few, are important factors in the uptake of iodines by the thyroid and the excretion into the milk. The excretion rates in the urine and feces will normally differ according to the species also.

VI. CONCLUSION

Numerous scientific investigations have been carried out in an attempt to develop a system for the prediction of fallout levels or the amount of contamination of the biosphere. The data have not always been satisfactory nor have the results been conclusive enough to predict, with any degree of accuracy, future fallout levels resulting from nuclear explosions under similar conditions. This limited ability to be able to predict levels of fallout is due to the many inherent unknowns that enter into the calculation of amounts of fallout as well as the inherent difficulties of measurement of the total fission release conditions.

It appears that if a study of any quality is to be attempted in the inhalation of radioiodines, it is unwise to assume that deposition of inhaled radioiodine is the same in the sheep as in the cow; that the percentage of uptake by the thyroid is the same in each cow of the herd; or that percentage of excretion in the milk is identical from one cow to the next under different conditions of season, diet and production. It is apparent from the survey of the literature that none of the results, under similar conditions of investigation, agreed well with each other. These results were for the most part from ^{131}I ingestion.

Therefore, in proposing areas of needed research in determining the potential hazard of radioiodines from inhalation, consideration will be given to species, season, diet, climate, topography, etc. It is understood that every animal to be used must be shown to be free of signs and symptoms of any infectious disease, free of physical defects, and having all physiological parameters being measured within normally acceptable limits.

VII. SUGGESTED EXPERIMENTS FOR THE STUDY OF POTENTIAL HAZARDS FROM INHALATION OF RADIOIODINES

In general, recommended experiments will make comparisons of different routes of administration of ^{131}I in various mammalian species particularly dairy cows and dogs. Following the interpretation of the experimental results of the kinetics of ^{131}I uptake and excretion and normal physiological limits of variance under the existing laboratory and field conditions, more sophisticated approaches to the inhalation of fresh fission products will be suggested. The species of choice will depend on what physiological parameter of interest is to be measured. The one chosen will, if possible, fall within the normal limits of man. Other related parameters will also be measured under similar experimental conditions for possible use in evaluation of potential hazards from inhalation of radioiodines. The following recommendations will attempt to follow a pattern of investigation that will give each succeeding experiment a sound physiological foundation. Recommendations for determination of certain physiological limits of deposition, retention, translocation and excretion of inhaled radioiodines are given below:

A. FIELD TYPE EXPERIMENTS

1. Determine the minimum quantity of fresh fission products, especially radioiodines, in a field aerosol that could be subsequently detected in measurable amounts in the thyroid and/or milk of the dairy and beef cow and of the rat.

2. Using dairy cattle, determine the biological half life, excretion and ratio in thyroid to milk, total dose to thyroid, and total dose to milk of radioiodines following ingestion of feed exposed to fresh fission products in the field.

3. Following exposures of dairy cattle and/or feed to field aerosols, determine quantitatively the differences in radiation dose from inhalation only, ingestion only, and a combination of inhalation and ingestion.

4. Determine food consumption per gram of thyroid in cattle which have been raised on typical dairy and beef farms and ranches in and near the Great Basin region.

5. Determine lung, body, and thyroid weight for different breeds and ages of dairy cattle, beef cattle and sheep that have been raised in the Great Basin region.

6. Determine relationship of levels of radioiodine in milk versus levels in sheep thyroids at the same geographical location.

7. Determine the relationship of gamma and gamma plus beta levels of forage (contaminated with fresh fission products and fed to dairy cows) to the thyroid uptake and milk excretion.

8. Determine the respiration rate, temperature and pulse of individual dairy cows and dogs by implantation of telemetric apparatus so that field data can be correlated with laboratory findings.

B. LABORATORY TYPE EXPERIMENTS

1. Determine deposition of fresh fission products and carrier free ^{131}I in the lungs of an intact animal (dog and cat) by lung scanning, followed by lung scanning of the sacrificed animal and followed in turn by lung scanning of the removed lungs.

2. Using dairy cows and dogs, determine the biological half life, excretion, ratio in thyroid and milk to total dose of carrier free ^{131}I and fresh fission products following intravenous, oral, intratracheal or inhaled routes of entry.

3. Determine the minimum air concentration of ^{131}I or fresh fission products necessary for its subsequent appearance in measurable amounts in the thyroid of rats.

4. Determine limits of normal dietary stable iodine in cattle feed which will not abnormally influence the uptake or excretion of fresh fission products and carrier free ^{131}I.

5. Determine respiratory minute volume per gram of thyroid in dairy and beef cattle and dogs.

6. By dosimeter implantation, determine tissue dosage to the thyroid and parathyroid glands of dairy or beef cows following ingestion and/or inhalation of fresh fission products.

7. Determine absolute and functional respiratory dead space at various respiratory velocities in dogs.

8. Determine tissue distribution of fresh fission products as a function of time following various routes of administration in the cow and dog.

9. Determine extent of participation eructation plays in the absorption of ^{131}I from the rumen.

10. Determine dose-response curves relating changes in pulmonary flow resistance produced by exposure to different levels of ^{131}I in aerosols.

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APPENDIX

Table 1. Fission product radioiodine chains.*

Mass Number	Atomic Number 49(In)	50(Sn)	51(Sb)	52(Te)	53(I)	54(Xe)	55(Cs)	56(Ba)
129	1.5 sec →	6.2 min →	4.2 hr	64% → 70 min	→ 1.6x10^7 yr	→ Stable		
			36% →	32 day				
131	1 sec →	3 sec →	23 min	95% → 25 min	→ 8.05 day	12% → Stable		
			5% →	30 hr	22% → 78%	88% → 12 day		
132		2.5 sec →	2 min →	78 hr →	2.3 hr →	Stable		
133		2 sec →	4.5 min	28% → 2 min	→ 20.8 hr	98% → 5.3 day	→ Stable	
			72% →	63 min	2% →	2.3 day		
134			10 sec →	44 min →	52.5 min	→ Stable		
135			6 sec →	10 sec →	6.7 hr	70% → 9 hr	3% → 2x10^6 yr	→ Stable
					30% →	15 min	97% → 3x10^{-10} sec	

*Reference: 65

Table 2. Activities of the radioiodines and tellurium-132 expressed as a fraction of the activity of iodine-131 for various decay times.*

FISSION PRODUCT	1 HOUR		10 HOURS		1 DAY		1 WEEK	
	Reactor	Criticality	Reactor	Criticality	Reactor	Criticality	Reactor	Criticality
^{132}Te	1.01	5.50	0.98	3.30	0.90	2.95	0.43	1.25
^{131}I	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
^{132}I	1.06	8.50	1.00	3.57	0.93	3.05	0.43	1.30
^{133}I	1.46	22.0	1.15	15.4	0.75	10.3	0.01	0.17
^{134}I	1.38	378	-	0.43	-	-	-	-
^{135}I	1.34	84.5	0.54	19.7	0.13	5.41	-	-

*Reference: 35

Table 3. Iodine isotopes formed in fission.*

Iodine Mass	Half Life	Parent Nuclide	Cumulative yields from smoothed urine ^{235}U	Cumulative yields from smoothed urine ^{239}Pu
124	4 days	Primary products of high energy fission bismuth and lead not found in fission at moderate energies.		
125	56 days			
126	13.0 days			
127	Stable	90 days Te-127m 9.3 hr Te-127	0.15	0.38
**				
129	1.72×10^7 years	32 days Te-129m 72 min Te-129	0.90	1.6
**				
131	8.04 days	30 hr Te-131m 25 min Te-131	2.80	3.7
132	2.4 hr	77 hr Te-132	3.4	4.8
133	22 hr	60 min Te-133	4.7	5.0
134	51 min	43 min Te-134	5.9	5.3
135	6.7 hr	Either primary	6.0	5.6
136	86 sec	fission products	6.1	5.8
137	22 sec	or formed from	6.2	5.9
138	5.9 sec	very short-lived	6.2	5.9
139	2.7 sec	tellurium parents.	6.1	5.9

*Reference: 82

**I-128 and I-130 (which have not been reported in fission) are shielded by Stable Te-128 and Te-130 respectively.

Table 4. Iodine activity and dose to the thyroid versus time after 10^{20} instantaneous fissions of ^{235}U.*

Iodine Mass Number	T_{eff} (days)	E_{eff} (Mev)	1 HOUR I_o (Curies)	1 HOUR $I_o/I_{(\%)tot}$	1 HOUR $D_o/D_{(\%)tot}$	3 HOURS I_o (Curies)	3 HOURS $I_o/I_{(\%)tot}$	3 HOURS $D_o/D_{(\%)tot}$
131	7.6	0.23	.45	.211	4.8	64	.553	8.3
132	0.097	0.65	380	1.79	1.5	275	2.39	1.3
133	0.87	0.54	1100	5.19	31.8	1250	10.8	43.4
134	0.036	0.82	16000	75.4	28.9	7000	60.4	15.2
135	0.28	0.52	3700	17.4	33.1	3000	25.9	32.2
Total			21225		100.1	11589		100.4
			6 HOURS			12 HOURS		
131			71	1.66	11.7	71	2.76	15.4
132			265	6.19	1.6	250	9.73	2.0
133			1250	29.2	55.4	1050	40.8	61.1
134			500	11.6	1.4		Negligible	
135			2200	51.4	30.1	1200	46.6	21.6
Total			4286		100.2	2571		100.1

continued

Table 4. Iodine activity and dose to the thyroid versus time after 10^{20} instantaneous fissions of ^{235}U. *(cont')

Iodine Mass Number	24 HOURS			2 DAYS			3 DAYS		
	I_o (Curies)	I_o/I_{tot} (%)	D_o/D_{tot} (%)	I_o (Curies)	I_o/I_{tot} (%)	D_o/D_{tot} (%)	I_o (Curies)	I_o/I_{tot} (%)	D_o/D_{tot} (%)
131	71	5.25	23.6	71	11.4	40.8	68	14.6	52.4
132	220	16.2	2.5	170	27.4	3.6	155	34.4	4.4
133	720	53.3	64.3	350	56.4	54.3	190	42.1	40.6
134	Negligible			Negligible			Negligible		
135	340	25.1	9.4	29	4.68	1.4	40	8.87	2.6
Total	1351		99.8	620		100.1	451		100.0
	4 DAYS			5 DAYS			7 DAYS		
131	63	21.5	66.6	58	30.8	83.1	50	43.5	93.4
132	130	44.4	4.97	100	53.1	5.2	60	52.2	4.0
133	100	34.1	28.4	30	15.9	11.6	5	4.35	2.5
134	Negligible			Negligible			Negligible		
135	0.45	0.15	0.04	0.23	0.12	0.02	Negliginle		
Total	293.4		100.01	188.2		99.92	115		99.9
	10 DAYS								
131	39	54.6	96.8						
132	32	45.8	2.9						
133	0.35	0.49	0.2						
134	Negligible								
135	Negligible								
Total	71.35		99.9						

*Reference: 107

Table 5. Iodine chemical forms*

Valence	Common Chemical Species
-1	I^-, HI, NaI, HI n H_2O
0	I_2
+1	ICI, IB2, HOI
+5	I_2O_5, IO_3^-, HIO_3, $NaIO_3$
+7	IO_4^-, HIO_4, $NaIO_4$
Organic	CH_3I, CH_2I_2, CHI_3, C_2H_5I, $C_2H_4I_2$

*Reference: 65

Table 6. Physical form of I-131 in air at various distances from stocks of a chemical separation processing plant.*, **.

Distance from Source, Miles	Percent Particulate ***
1	12
3	8
5	20
10	34
20	38
25	34

*Reference: 97
**Hanford Laboratory, G. E. Company, Hanford, Washington.
***Sampled by aircraft 600' above ground.

Table 7.* Deposition processes and the size ranges of importance in each.**

Process	In Environment		In Respiratory Tract	
	Lower Limit	Upper Limit	Lower Limit	Upper Limit
Sedimentation	0.5μ	None	0.5μ	30 μ
Impaction	0.2μ	None	0.2μ	30 μ
Brownian motion	50 Å	0.1μ	50 Å	0.1μ
Thermal precipitation	50 Å	0.1μ	Not important	
Electrostatic precipitation	50 Å	0.1μ	Not important	
Condensation	0.1μ		0.1μ	
Aggregation	All sizes		All respirable sizes	

*Reference: 42

**Values for upper and lower limits are approximate.

Table 8. The lung volumes and capacities.*

A. VOLUMES. - There are four primary volumes which do not overlap (Figure 2):

1. Tidal Volume, or the depth of breathing, is the volume of gas inspired or expired during each respiratory cycle.
2. Inspiratory Reserve Volume (formerly complemental or complementary air minus tidal volume) is the maximal amount of gas that can be inspired from the end-inspiratory position.
3. Expiratory Reserve Volume (formerly reserve or supplemental air) is the maximal volume of gas that can be expired from the end-expiratory level.
4. Residual Volume (formerly residual capacity or residual air) is the volume of gas remaining in the lungs at the end of a maximal expiration.

B. CAPACITIES. - There are four capacities, each of which includes two or more of the primary volumes (Figure 2):

1. Total Lung Capacity (formerly total lung volume) is the amount of gas contained in the lung at the end of a maximal inspiration.
2. Vital Capacity is the maximal volume of gas that can be expelled from the lungs by forceful effort following a maximal inspiration.
3. Inspiratory Capacity (formerly complemental or complementary air) is the maximal volume of gas that can be inspired from the resting expiratory level.
4. Functional Residual Capacity (formerly functional residual air, equilibrium capacity or mid-capacity), is the volume of gas remaining in the lungs at the resting expiratory level. The resting end-expiratory position is used here as a base line because it varies less than the end-inspiratory position.

*Reference: 22

Table 9. Composition of alveolar air of several species.

Species	Number	CO_2%	O_2%	pCO_2 mm Hg**	pO_2 mm Hg***	Reference
Horse	1*	4.93	15.09	35.4	107.4	41
	-	4.74	15.97	-	-	39
Cattle	3*	4.75	15.40	34.2	107.4	41
Sheep	3*	4.59	15.65	33.65	114.4	41
Goat	3*	5.18	15.04	38.0	110.4	41
	-	2.95	17.80	-	-	39
Dog	3*	5.32	14.99	39.0	108.6	41
Man	-	4.21	16.29	40	106	39

*Five different measurements on each animal.
**Vapor pressure of CO_2 in mm Hg in the alveolus.
***Vapor pressure of O_2 in mm Hg in the alveolus.

Table 10. Ventilation and complementary cycles of various species.*

Species	Body Weight Kg	f**	Ventilation Cycle		Complementary Cycle		
			Tidal Volume in ml	Duration in secs	f/hour	Volume in ml	Duration in secs
Mouse	0.015	125	0.1	0.5	45	4.7	4
Rat	0.273	60	1.4	1.0	26	-	5
Guinea Pig	0.495	84	1.9	0.7	17	-	7
Rabbit	3.0	66	18.3	0.9	10	-	6
Cat	2.6	26	12.4	2.3	6	-	9
Dog	19.2	14	110.0	4.3	5	-	7
Man	70	16	500.0	3.5	3	-	8
Horse (Standardbred)	550	12	6000	5.0	0	-	0

*Reference: 83
**Respiratory frequency

Table 11. Diameter of alveoli of various species.

Species	Number	Mean Diameter in μ	Reference
Feline	21	116.9±14.4	113
		133.2	29
Canine	8	93.9±14.1	113
		74.1	29
Guinea Pig	14	65.4±8.5	113
		83.4	29
Mouse	6	46.6±2.4	113
		38.7	29
Rat	17	70.2±6.6	113
		59.1	29
Monkey	-	89.1	29
Man	-	166.1	29
1-1.5 years	-	100	60
18-20 years	-	200	60
50-60 years	-	300	60
	-	150	33

Table 12. Tidal volume frequency and compliance of various species.

Species	Number Measured	Body Weight in kg	V_t[1] ml	f[2]	V_m[3] ml	Compliance ml/cm H_2O	Reference
Mouse	14	0.024	0.15	154	23.1	0.029	38
	7	0.024	0.13±0.06	210±50	27.3±3	-	47
	5*	0.023	0.09±0.06	120±60	10.8±3.6	-	47
	-	0.032 (0.037-0.038)	0.18 (0.09-0.38)	109 (97-123)	21 (9-46)	0.049 (0.025-0.068)	29
	-	0.0198	0.15 (0.09-0.23)	163 (84-230)	23 (11-36)	-	60
	56	0.198 (0.012-0.026)	0.15 (0.09-0.23)	163 (84-230)	24.5 (11-35.8)	-	58
	-	0.88±0.12	-	75	-	1.5±0.14/kg	1
	-	0.69 (0.43-1.05)	3.7 (2.3-5.3)	42 (16-67)	130 (80-190)	1.26 (0.76-2.33)	29
	-	0.47	1.8	90 (69-104)	160 (90-380)	-	60
	61	0.466 (0.274-0.941)	1.75 (1.0-3.9)	90 (69-90)	155 (100-382)	-	58

Table 12. Tidal volume frequency and compliance of various species. (Cont')

Species	Number Measured	Body Weight in kg	V_t [1] ml	f [2]	V_m [3] ml	Compliance ml/cm H_2O	Reference
Monkey	6	2.68 (2.0-3.08)	21.2 (9.8-29.1)	40 (31-52)	863 (311-1410)	-	58
	-	2.45 (1.8-3.05)	20 (9-29)	33 (27-47)	700 (260-1340)	12.3 (7.1-20.2)	29
	-	2.68	21 (9.8-29)	40 (31-52)	860 (310-1410)	-	60
Rat	9	0.203	1.3	80	97	0.148	38
	-	0.25 (0.19-0.32)	1.55 (1.03-2.13)	97 (84-126)	160 (90-270)	0.39 (0.22-0.52)	29
	-	0.112	0.86 (0.60-1.25)	85 (66-114)	74 (50-102)	-	60
	35	0.112 (0.063-0.52)	0.86 (0.60-1.25)	85 (66-114)	72.9 (49.8-101.2)	-	58
	-	0.207±0.007	-	110	-	1.94±0.04/kg	1
Man	?	70	500	15	7500	85	38
	-	70	400	16	6400	-	29
	-	70	-	-	-	120	60
	*	60	-	-	-	62	60
	-	70	-	15	-	2/kg	1
	10	68.5 (55.7-82.1)	616 (315-745)	14 (10.5-19.3)	8732 (4900-12200)	- -	58

Table 12. Tidal volume frequency and compliance of various species. (Cont')

Species	Number Measured	Body Weight in kg	V_t[1] ml	f[2]	V_m[3] ml	Compliance ml/cm H_2O	Reference
Dog	15	16.3±4.3	16±5.8ml/kg	26±13	6656	4.6±1.54/kg	23
	3	17	107	22	2354	30	38
	12*	18.3±5.6	228 12.5±2.5 ml/kg	46±15	10488	63±20	86
	39*	13.4±5	247±17	28±3	4199±51	50.8±3	4
	-	12.6 (10.0-15.5)	144 (122-176)	21 (6-31)	2300 (800-3500)	40 (27-61)	29
	*	20	-	-	-	48	60
	*	11.8	-	-	-	26.5	60
	4	23.6	320	17 (11-21)	5200 (3300-74000)	-	60
	-	10.4±0.48	-	18	-	2.56±0.3/kg	1
Rabbit	3	2.6	16	38	608	2.4	38
	-	2.4 (2.05-3.0)	15.8 (11.5-24.4)	39 (32-53)	620 (370-890)	6.0 (3.5-10.8)	29
	*	2	-	-	-	2.3	60
	-	2.98±0.31	-	50	-	1.41±0.19/kg	1
	-	2.07	-	-	800 (270-1200)	-	60
	-	-	20	61	12300	-	60

Table 12. Tidal volume frequency and compliance of various species. (Cont')

Species	Number Measured	Body Weight in kg	V_t [1] ml	f [2]	V_m [3] ml	Compliance ml/cm H_2O	Reference
Rabbit(cont')	31	2.069 (0.79-3.09)	-	-	800 (270-1208)	-	58
Horse	-	430	-	-	-	800	60
	1	696	9060 (8520-9680)	11.9	107 L	-	60
	19*	28±3	286±25	24.5±2	-	57±6	4
	-	225	-	-	37 L	-	60
Cat	-	3.54±0.32	-	30	-	2.86±0.28/kg	1
	-	3.7 (2.3-5.7)	34 (20-42)	30 (24-42)	960 (860-1090)	13.4 (9.9-17.4)	29
	*	3.2	-	-	-	6.8	60
	*	2.6	-	-	-	5.7	60
	-	2.45	12.4	26	322	-	60
Cow	4(lying)	439	3200	30	96 L	-	60
	4(standing)	439	3800	28	106 L	-	60
Sheep	50*	42.6±4.7	249±51**	-	-	106±31	59
	-	63	310	19	5700	-	60
Goat	-	-	-	28	-	-	70
	1	37	-	-	-	50	5

*Anesthetized
**Tidal volume in ml/M^2
1 - Tidal volume in ml 2 - Respiratory frequency 3 - Minute volume

Table 13. Distribution of inhaled particles.*

Distribution	Readily "Soluble" Compounds	Other Compounds
	(%)	(%)
Exhaled	25	25
Deposited in upper respiratory passages and subsequently swallowed.	50	50
Deposited in the lungs (lower respiratory passages).	25**	25***

*Reference: Recommendations of International Commission on Radiological Protection. Brit. J. Radiol. Supp. 6, 1955 (from 42)

**This is taken up into the body almost immediately.

***Of this, half is eliminated from the lungs and swallowed in the first 25 hours making a total of 62.5% swallowed. The remaining 12.5% is retained in the lungs with a half-life of 120 days, it being assumed that this portion is taken up into the body fluids.

Table 14. Retention of ^{15}O water vapor in three human subjects.*

Region of Respiratory Tract	Activity Counts/sec.	Percent of Total Activity
Mouth	170	28.9
Pharynx	120	20.4
Upper trachea	160	27.4
Mid trachea	100	17.0
Corina	33	5.8
Right lung base	3	0.5

*Reference: 118

Table 15. Average values for thyroid size, iodine content and biological half-life of thyroid iodine in different species.*

Species	Thyroid Size		Thyroid Iodine	
	Gram	mg/kg Body Weight	mg	Biological Half Life in Days
Cattle	18	45	8-16	16
Swine	15	80	6-20	30
Lamb	2	50	1-3	14
Rat	0.02	80	0.02	4
Man	25	360	8	94

*Reference: 115

Table 16. Forty-eight hour uptake of ^{131}I* by thyroid gland of dairy calves.**

Breed	Number	Average Age Months	Uptake %	Standard Deviation
Ayrshire	2	6.2	42.5	-
Brown Swiss	19	4.2	33.2	18.3
Guernsey	7	6.7	47.9	21.6
Holstein	19	3.5	44.1	15.8
Jersey	16	5.8	45.8	19.9

*Injected subcutaneously
**Reference: 80

Table 17. Comparison of rate and percentage uptake of radioiodines.

Animal	Isotope	Method of Administration	Effective Half Life in Days	Time of Maximum Uptake in Hours	Percentage Uptake	Reference
Sheep	^{131}I	Oral	6.5-8	48-96	17-19	123
	^{131}I	Intravenous	6.5-8	48-96	17-19	123
	^{131}I	Subcutaneous	6.5-8	48-96	17-19	123
	^{131}I	Topical	7	48-96	2-14	123
	^{131}I	Inhaled	-	20-35	3-8	121
	Ag ^{131}I	Inhaled	-	20-24	3-8	121
Mice	^{131}I vapor	Inhaled	-	30	2.5	121
	Ag ^{131}I	Inhaled	-	10	1.6	121
Dog	^{133}I and fiss. prod.	Inhaled	Short	48-72	92	48
Cattle	Na ^{131}I	Subcutaneous	-	48	41.6	80
	^{131}I	Oral	4.5	30	35	18
Swine	^{131}I	Oral	6.5	24	30	17
Rat	^{131}I	Inhaled	-	44	26.9	13
Man(neonatal)	^{131}I	Oral	-	48	62	45
2 mos-18 yrs	^{131}I	Oral	-	24-48	31 ± 7.63	45
Adults	^{131}I	Oral	-	24	36 ± 9.9	45

Table 18. Fate of ^{131}I in the dairy cow.

Route of Elimination	Method of Administration	Percent of Dose	Recovery Period (Days)	Reference
Thyroid	Oral	15±6.0	7	24
	Intravenous	18	3-5	111
Milk	Oral	6.2±2.0	1	24
	Intravenous	7.2	3	111
	Oral	3.28	6	108
Urine	Oral	55±14	7	24
	Intravenous	43.7	3	111
	Oral	27.8	6	108
Feces	Oral	17±7	7	24
	Intravenous	17.6	3	111

Table 19.* Translocation of iodine-131 following inhalation.**

Tissue	$Ag^{131}I$		^{131}I	
	Immediately	10 Hour***	Immediately	30 Hour***
Lung	45	9	15	0.7
Bone	-	-	-	-
Thyroid	750	6800	130	1700
Liver	17	5	20	0.7
Lymph	36	48	67	2.2
Spleen	36	5	17	0.17
Adrenal	43	13	20	0.6
Kidney	18	11	25	1.0
Ovary	108	38	150	3.5

*Reference: 7

**Percentage of total deposited per gram tissue at various times after inhalation.

***Time of maximum concentration in thyroid.

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