

RADIONUCLIDE EXPOSURE OF THE EMBRYO/FETUS

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RADIONUCLIDE EXPOSURE OF THE EMBRYO/FETUS

**Recommendations of the
NATIONAL COUNCIL ON RADIATION
PROTECTION AND MEASUREMENTS**

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7910 Woodmont Avenue, Suite 800, Bethesda, MD 20814-3095**

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Preface

The National Council on Radiation Protection and Measurements (NCRP) has had a longstanding interest in radiation exposures of the embryo/fetus. Recommendations regarding the embryo/fetus were published in 1954 in NCRP Report No. 17 (published as National Bureau of Standards Handbook 59). Those recommendations, as well as those in NCRP Report No. 39 in 1971, NCRP Report No. 53 in 1977, and NCRP Report No. 91 in 1987, limited the maximum permissible exposure to the embryo/fetus to the same annual limit used for the general population. The current limit recommended in NCRP Report No. 116 for the exposure of the embryo/fetus is 0.5 mSv per month once the pregnancy is known.

Radionuclides that enter the mother's body can irradiate the embryo/fetus from sites of deposition within the mother's body and can be transferred to the embryo/fetus and irradiate it directly. Radionuclide content and concentrations within the embryo/fetus are difficult to estimate and are, therefore, generally imprecise. Calculations of radiation absorbed doses from the radionuclides, once the contents are known, also involve considerable uncertainties. Given these uncertainties the dose received by the embryo/fetus, per unit intake in the mother, are inherently uncertain.

However, in view of the potential intake of radionuclides by female workers and female members of the public, this Report is designed to provide information on radiation doses to the embryo/fetus. It describes aspects of prenatal development that affect the disposition of radioactive materials that enter the embryo/fetus, summarizes current knowledge about the placental transfer of these radionuclides and their biokinetics in the mother and in the embryo/fetus, and describes approaches for estimating radiation doses to the embryo/fetus. An appendix presents specific physical and biological data on a large number of individual radionuclides.

This Report has been reviewed and approved for publication by the Council. The material contained in this Report was prepared by Scientific Committee 57-14 on Exposure of the Embryo/Fetus from

Radionuclides in the Pregnant Woman. Serving on the Committee during the preparation of the draft material were:

Melvin R. Sikov, Chairman
Pacific Northwest National Laboratory
Richland, Washington

Members

James S. Robertson
Gaithersburg, Maryland

Audrey V. Wegst
Diagnostic Technology
Consultants
Mission, Kansas

Evelyn E. Watson
Oak Ridge Associated Universities
Oak Ridge, Tennessee

Consultant

Keith F. Eckerman
Oak Ridge National Laboratory
Oak Ridge Tennessee

NCRP Secretariat

Thomas M. Koval (1993-1998), *Senior Staff Scientist*
E. Ivan White (1985-1993), *Senior Staff Scientist*
Cindy L. O'Brien, *Editorial Assistant*

The Council wishes to express its appreciation to the Committee members for the time and effort devoted to the preparation of the Report.

Charles B. Meinholt
President

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1. Introduction

1.1 Purpose

Information on the response of the mammalian conceptus to radiation has been periodically evaluated by various organizations. The general conclusions of these evaluations are summarized in Section 1.3. Several of these organizations have published recommendations or regulations concerning radiation doses to pregnant women and the embryo/fetus. These recommendations or regulations are reviewed in Section 3 of this Report.

The purpose of this Report is to provide information about radiation doses to the embryo/fetus and the effects of radionuclide exposure during pregnancy. The dosimetry of external sources is beyond the scope of this Report and is not addressed. The Report describes aspects of prenatal development that affect the disposition of radioactive materials that enter the embryo/fetus. It summarizes current knowledge about the placental transfer of these radionuclides and their biokinetics in the woman and in the embryo/fetus. Approaches are described for estimating radiation doses to the embryo/fetus that result from radionuclide burdens or intakes by a pregnant woman that relate to occupational, medical and environmental sources of radioactive material. In addition, these analyses lead to comparisons among interpretations of dose from internally deposited radionuclides to the embryo (the conceptus from fertilization through organogenesis) and to the fetus (post-organogenesis through birth).

1.2 Scope

Insofar as possible, all available reports relating to placental transfer of radionuclides and their concentrations and dosimetry in the human embryo/fetus were reviewed for relevant data. It will become evident, however, that this database is not extensive. The text is directed at providing the reader with the basic background needed to appreciate the rationale for derivations of numerical values, the uses and limitations associated with these values, and the

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factors involved in deriving recommendations concerning dosimetry. Only a few calculations were developed for this Report to illustrate approaches. Some quantitative results are included in Appendix A, which presents examples and values from the literature that may be useful in dose estimation. Environmentally relevant radionuclides are considered as well as radionuclides that could be expected to be relevant to women in their work environment or as patients undergoing nuclear medicine procedures.

Many of the data regarding placental transfer and the resulting radionuclide content in the human conceptus have been obtained from exposures of pregnant women to labeled metabolites or radiopharmaceuticals (Bowen *et al.*, 1992; ICRP, 1987). Additional data about radionuclides of occupational and environmental interest have been obtained from radioanalyses of embryonic and extra-embryonic tissues, abortuses, neonatal decedents, and placentas (Sikov *et al.*, 1992a). Interpretations of such data may be clouded by uncertainties regarding the magnitude and time of intake and hence maternal burden. Still other information, primarily applicable to calculation of kinetics, has been obtained through *in vitro* studies using perfused human placentas (Kelman and Walter, 1980; Young *et al.*, 1981).

The scarcity of data on placental transfer and fetoplacental distribution obtained from analyses of human materials makes it necessary to extrapolate from studies of animals. Many of these data are derived from experiments in which terminal measurements of fetoplacental radionuclide concentrations were performed as adjuncts to studies involving assays of embryotoxicity: prenatal mortality, decreased prenatal growth, and teratogenesis. More recent studies, which provide a basis for calculating kinetic parameters, have been directed at measuring radionuclide concentrations in maternal blood and tissues, throughout the placental structures, and in tissues of the conceptus as a function of time after exposure. Other studies have investigated transport processes and mechanisms and examined factors that affect or modify placental transfer and fetoplacental distribution. This Report considers similarities and dissimilarities between the prenatal development, placental structure and function, and responses to acute external irradiation of laboratory animals and the human conceptus.

The size, shape and structure of the conceptus and the geometric factors that are of inherent importance in dose calculations undergo progressive change throughout development. The morphologic and physiologic development of the fetoplacental unit will be described in Sections 4 and 5, respectively. A synopsis of the effects

of prenatal irradiation, particularly relating to those produced by incorporated radionuclides, is presented in Section 6.

1.3 Background

Delineation of the effects of exposure to radiation during gestation has been the subject of research, reviews and analyses through the last several decades. Epidemiological re-evaluations of data concerning irradiated atomic-bomb survivors in Japan created additional concerns about ensuring adequate assessment and control of radiation exposure during human pregnancy (ICRP, 1986; Otake and Schull, 1984). Revisions in estimates of doses received by individual members of the Japanese population reopened questions regarding various measures of radiation risk and dose limits (NAS/NRC, 1990). Additional interest regarding prenatal radiation in the general population due to radionuclides was stimulated by the 1986 accident at Chernobyl.

National and international advisory bodies and regulatory agencies have published their evaluations of information about irradiation during pregnancy. Most of these reached similar conclusions although there are differences among details and estimates of risk (ICRP, 1977; 1986; 1991a; NEA/OECD, 1988a; NCRP, 1977a; 1977b; 1987a; 1993; 1994; UNSCEAR, 1986; 1993).

There is general agreement that the susceptibility to radiation-induced deterministic effects is higher in the mammalian embryo after implantation and in fetuses as compared to adults (Brent, 1980a; 1980b; Brent *et al.*, 1987; Konermann, 1987; NCRP, 1993; Streffer and Molls, 1987; UNSCEAR, 1977; 1986; 1993). The most striking radiation effect on development, malformations and congenital functional deficits of the central nervous system (CNS), in particular, are produced only by exposure during the prenatal period. Evaluations indicate a developmental-stage dependence for the induction of a spectrum of functional effects in the groups of Japanese children that received intrauterine exposure to lower doses, but elevated incidences of morphologic defects were not detected. While some organizations have published risk analyses that suggest that there might not be a threshold dose for diminution of mental capacity by prenatal exposure (ICRP, 1986; UNSCEAR, 1986), subsequent analyses have concluded that, based on mechanistic teratological considerations, a threshold should pertain (Brent, 1994; NEA/OECD, 1988a; Sikov, 1992a).

Other data used to evaluate risk to the human conceptus have been obtained from diagnostic exposures of pregnant women, but

interpretations of any deleterious effects are clouded by the circumstances that led to performing the diagnostic procedure. Numerous case reports and reviews of embryotoxic effects are available following radiation exposures of pregnant women to higher doses for a variety of medical reasons and from the higher dose groups in Japan (Dekaban, 1968; Miller, 1956; Yamazaki and Schull, 1990). These studies do not provide an adequate quantitative basis for assessing risk in the low-dose range associated with occupational, environmental or current diagnostic medical exposures. Accordingly, toxicity data obtained from experiments with laboratory animals are required to assess risk associated with radiation exposure during development. The usual uncertainties about extrapolating animal data to humans pertain to effects as well as to placental transfer.

Because of a pronounced dependence on dose and stage of gestation, the effects of radiation on the embryo/fetus cannot be adequately summarized by a simple statement. This limitation is particularly applicable when the source is internal, because the resulting prenatal radiation exposure depends upon many variables. Dose-effect relationships are affected by radiation type and energy, and the nature of embryonic and fetal effects and radiosensitivity are especially dependent on the stages of development during the exposure. Chemical form and other factors, which are usually considered in the dosimetry of internally deposited radionuclides in adults, also pertain to the embryo/fetus. A similar array of factors also determines the extent to which these materials are transferred across the placenta and incorporated into tissues of the conceptus. Major changes in the factors affecting dose take place during the transition from embryo to fetus at about eight weeks in the human.

2. Sources of Exposure

The embryo/fetus can be exposed to ionizing radiation in a variety of ways and under various circumstances. Radiation from sources outside the mother's body can impinge on the embryo/fetus and radioactive materials can enter the mother's body and the radiation emitted by them can irradiate the embryo/fetus from sites of deposition within the mother's body and the material can also be transferred to the embryo/fetus and irradiate it directly. Here, the focus will be on radiation from radionuclide materials that can gain access to the mother's body or the embryo/fetus itself. Radiation from sources outside the mother's body are not treated in this Report.

There are several exposure pathways that offer the potential for radioactive sources to gain entry into the body. The sources themselves can be divided into two categories, natural and man-made, and there are many ways by which each type can enter the human body. The natural sources encompass radionuclides present in the environment and these can be inhaled or ingested or gain entry *via* wounds. Included among the many natural radionuclides are ^{40}K , ^{14}C , and radon and radon daughter products which present the greatest potential for exposure of all humans.

Many man-made sources, when they are released to the environment, can follow the same exposure pathways as natural radionuclides but they also present a number of unique modes of exposure and thus it is appropriate to summarize these to make evident the many ways in which an embryo/fetus might be exposed.

Exposures of the embryo/fetus to man-made sources fall into two broad categories, those that arise from occupational activities of the mother and those that can occur to any member of the general public.

Among the many ways by which the embryo/fetus might be exposed as a result of the mother's occupational activities are her employment in activities such as (1) production and distribution of radiopharmaceuticals and other radionuclides, (2) treatment and handling of patients undergoing nuclear medicine procedures, (3) research involving the use of radionuclides, (4) nuclear power operations, (5) industrial activities involving the use of

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radionuclides, (6) cleanup and restoration of contaminated sites and facilities, and (7) radiation protection at facilities where radionuclides are used.

Among the ways the embryo/fetus might be exposed outside of an occupational setting are situations such as (1) maternal intake of natural radionuclides in the environment; (2) radionuclides administered to the mother for medical diagnosis or therapy; and (3) release of effluents by nuclear or coal-fired plants, reprocessing plants, and hospitals and laboratories; nuclear weapons detonations; releases attributable to cleanup of contaminated sites; accidental release of radionuclides; or exposure of the mother to contamination resulting from nuclear medicine procedures.

Many of the sources of exposure and pathways outlined above have been the subjects of detailed study and analysis, if not for examination of the potential exposure of the embryo/fetus, then for evaluation of the exposures of workers and members of the general public. For additional details, the reader is referred to the extensive literature (Alazarak and Mishkin, 1991; NAS/NRC, 1988; NCRP, 1987b; 1987c; 1987d; 1989a; 1989b; 1991a; 1991b; 1996; Phan *et al.*, 1987; Spengler, 1997; Stather *et al.*, 1984; Takahashi *et al.*, 1997; UNSCEAR, 1993).

3. Recommendations and Regulations

As mentioned in the Introduction, similar recommendations, rules and regulations concerning radiation exposures of the embryo/fetus have been issued by several national and international bodies. The general consideration is to limit the radiation dose received by the pregnant woman and the embryo/fetus and to avoid substantial variation in dose. There are differences among the statements depending on whether they relate to medical use of radiation, occupational exposures, or exposures to the general population. They also differ relative to national posture and the position that the issuing organization takes relative to dose calculation and expression.

The National Council on Radiation Protection and Measurements (NCRP) has had continuing concerns about radiation exposure of the embryo/fetus and has issued several reports that considered exposures of pregnant women. In NCRP Report No. 17 [published as NBS Handbook 59 (NCRP, 1954)], the NCRP determined that it was not necessary to recommend for pregnant women, a weekly dose lower than the basic permissible weekly dose to nonoccupationally exposed individuals, which at the time would have permitted 78 mSv in the first six months and 117 mSv in nine months of pregnancy (NCRP, 1954). In NCRP Report No. 39 (NCRP, 1971), the NCRP recommended that the maximum permissible dose equivalent to the embryo/fetus from occupational exposure of the expectant mother should be 5 mSv, which was the same value then used for the general population. This was reaffirmed in NCRP Report No. 53 (NCRP, 1977a). NCRP Report No. 54, which dealt with medical radiation exposures, emphasized the need for medical judgment and urged prudent use of procedures that involved potential exposure of the embryo/fetus (NCRP, 1977b). It noted, however, that many felt that 50 mGy would yield acceptable risk/benefit ratios. It was also observed that clinical evidence suggested that pregnancy termination need not be considered at doses below 50 mGy (NCRP, 1977b). The NCRP reiterated the 5 mSv dose

equivalent limit for the embryo/fetus in NCRP Report No. 91 (NCRP, 1987a).

3.1 Current Recommendations, Rules and Regulations

The International Commission on Radiological Protection (ICRP) has periodically presented refined concepts expressing tissue sensitivities to stochastic effects. In their Publication 60 (ICRP, 1991a), exposure was restated as effective dose and the recommended dose limit was 1 mSv for members of the public. For occupational exposure, the dose limit was a 50 mSv annual limit and 20 mSv y^{-1} , averaged over 5 y periods. ICRP Publication 60 also recommended a supplementary equivalent-dose limit to the abdominal surface of a woman after declaration of pregnancy of 2 mSv for the remainder of the pregnancy together with limiting radionuclide intakes to one-twentieth of the annual limit on intake (ALI).

In Report No. 116 (NCRP, 1993), the NCRP recommended that for occupational exposure of pregnant women (excluding medical and natural background radiation), the equivalent dose rate to the conceptus should be limited to 0.5 mSv in any month. NCRP also concurred with the recommendation of the ICRP that limited radionuclide intakes to one-twentieth of the annual reference limit on intake (ARLI) for the pregnant woman.

The administrative requirement in the United States for dose limitation during pregnancy is stated in the Federal Register as radiation protection guidance to federal agencies for occupational exposure (EPA, 1987). Consistent with the intent of that guidance, current limits for exposures for users licensed by the U.S. Nuclear Regulatory Commission (NRC), which is also used in agreement states, are given in 10 CFR Part 20 (NRC, 1991). There are no significant differences in the corresponding rules for facilities of the U.S. Department of Energy (DOE), which are given as 10 CFR Part 835 (DOE, 1997).

Current occupational dose limits in the United States are generally summarized by these statements from 10 CFR Part 20 (NRC, 1991): "The licensee shall ensure that the dose to an embryo/fetus during the entire pregnancy, due to occupational exposure of a declared pregnant woman, does not exceed 0.5 rem (5 mSv). The dose to an embryo/fetus shall be taken as the sum of the deep-dose equivalent to the declared pregnant woman and the dose to the embryo/fetus from radionuclides in the embryo/fetus and

radionuclides in the declared pregnant woman." The provisions above do not apply until a formal declaration of pregnancy is made.

3.2 Perspective and Related Activities

In the mid-1980s, the NRC, recognizing that adequate approaches were not available for making dose calculations to the embryo/fetus and the mother for radionuclides, instituted a project at DOE's Pacific Northwest Laboratory to develop methodologies and calculations. That project prepared a report, NUREG/CR-5631 (PNL-7445), Rev. 1 (Sikov *et al.*, 1992b), to provide the input to Regulatory Guide 8.36 that formalized approaches to calculation of dose to the embryo/fetus from radionuclides (NRC, 1992). Addenda and revisions were made to provide biokinetic models and dosimetric information for radionuclides and compounds of importance. This information was integrated into the last revision of the NUREG (Rev. 2) that is cited in this Report as Sikov and Hui (1996) and which provides some of the biokinetic and dosimetric results that are incorporated into Appendix A of this Report.

Also in the 1980s, prenatal radiation doses from radiopharmaceuticals used in nuclear medicine were being investigated at the Oak Ridge Institute for Science and Education (Watson *et al.*, 1992a; 1992b). Moreover, the NCRP had initiated the study which resulted in this Report and this activity operated concurrently and in concert with the other efforts. The initial goal of the NCRP effort was to address the placental transfer of radionuclides; subsequently, the scope was expanded to provide the additional information on dosimetry and biological effects as presented in this Report.

The massive release and widespread dispersion of radioactivity following the accident at Chernobyl increased awareness of uncertainties in assessing radiation doses to the embryo/fetus and to juvenile members of the general population from internally deposited radioactive materials. This led to increased research efforts and international symposia that are described in reports and volumes such as UNSCEAR (1986), Gerber *et al.* (1987), and Taylor *et al.* (1992). These efforts were integrated with activities by the ICRP that resulted in ICRP Publications 56 and 67 (ICRP, 1989; 1993).

3.3 Expression of Prenatal Doses as Exposure Limits

Estimation of radionuclide content or concentrations in the conceptus is difficult and imprecise. Calculation of average radiation absorbed doses from these quantities involves further uncertainties. Moreover, radiation doses to individual organs usually cannot be determined by dosimetric techniques that are in current use and directed research is required.

Derived quantities such as committed or effective dose, which currently are relevant to stochastic effects of irradiation of adults, are considered in Section 7. This Report will not attempt to use this approach for the embryo/fetus because organ doses are not yet available and the applicability of adult tissue weighting factors (w_T) to the conceptus has not been established. Exposure of the embryo/fetus will be expressed as the radiation absorbed dose received during the intrauterine period. It is assumed that dose values may be multiplied by the same quality factors or radiation weighting factors (w_R) used for adults to obtain dose equivalent or equivalent dose (see Section 7).

4. Prenatal Development

The stage of development of the embryo/fetus at the time of irradiation is a major factor affecting its radiosensitivity, the spectrum of expected effects, and the extent to which materials are transferred across the placenta. Detailed considerations of comparative reproductive biology or prenatal development are beyond the scope of this Report. However, descriptions will be presented to provide adequate familiarity with placental and embryo/fetal development for appreciation of the stage-dependent changes in placental transfer, dosimetry and radiation response.

Gestational ages are usually expressed relative to time elapsed after conception (fertilization), which occurs within hours after copulation and this will be the convention used in this Report. It should be noted, however, that time in human pregnancies is sometimes (especially in clinical situations) counted from the last menstrual period, which precedes conception by about two weeks.

Gestation is customarily divided into a limited number of broad periods or stages for generalized consideration of teratogenic agents. The additional impact of dosimetric factors make this approach especially convenient for discussing external irradiation and internally deposited radionuclides. Most information on human placental transfer and radiation effects has been derived from experiments with mice and rats, although confirmatory data have been obtained from studies of other species, including human populations. There are genetically related quantitative variations among relevant reproductive measures in the human and commonly used animal species, but typical values are summarized in Table 4.1.

To illustrate the range of species-related similarities and differences, Figure 4.1 provides a simplification of a diagrammatic representation that was presented by UNSCEAR (1986). The corresponding stages of rat, guinea pig, and human development are shown to cover the relevant range of developmental stages.

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Table 4.1—*Typical values of reproductive measures for comparisons between the human and common experimental animal species.*

Measure	Human	Monkey (rhesus)	Rat (outbred)	Mouse (outbred)	Hamster	Guinea Pig
Fertilization to birth (d)	270	168	22	19	16	68
Birth weight ^a (g)	3,400	600	7	2	2.2	85
Weight ^a relative to mother (%)	5.8	6	2.2	6	2.3	9.4
Typical number of offspring per pregnancy	1	1	10	10	12	2

^a Weight per offspring.

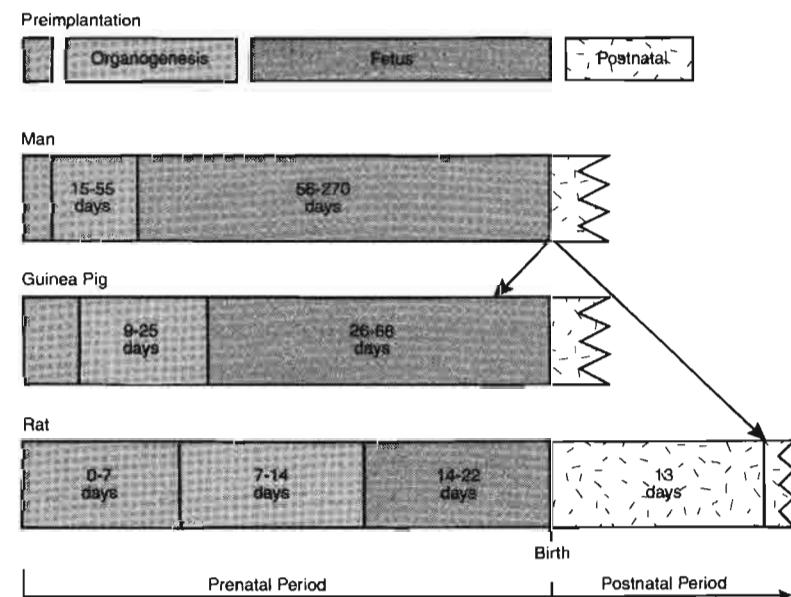


Fig. 4.1. Comparison of fractional length of major developmental periods during prenatal development of the human, guinea pig, and rat. The abscissa indicates percentage of gestation or the neonatal period on a linear scale. The arrows point to the fractional times at which development of the guinea pig and rat correspond to the human at birth.

Further details for these species and others were summarized from various sources and are presented in Table 4.2 (Altman and Dittmer, 1962; Butler and Juurlink, 1987; Otis and Brent, 1954; Shepard, 1992).

As has been described in embryology textbooks, the general sequence of developmental stages is the same across mammalian species (Arey, 1946; Langman, 1974; Moore, 1988). The stages differ in their relative length and relationships to chronological times of gestation and the degree of maturity at birth differs, even among related species such as the rat and guinea pig (Butler and Juurlink, 1987). Accordingly, it is necessary to consider relative maturities, the times that major events occur, and when structures develop in making comparisons and extrapolations.

The fetal guinea pig attains an overall degree of development comparable to the newborn human at a time prior to birth, but the rat does not reach a generally comparable stage until during its second week of postnatal life. Moreover, the times of attaining equivalent measures of development of major tissues important in radionuclide disposition, such as thyroid function and skeletal ossification, do not have identical temporal relationships to these developmental landmarks. These differences are of concern relative to specific comparisons and extrapolations but a satisfactory approach has not been developed to completely integrate this consideration into analyses. Also, developmental stage at the time of irradiation is an important factor in estimating the effect. Therefore, it should be emphasized that absolute and relative lengths of the period of organogenesis, which is the stage that is most susceptible to teratogenic effects, varies among species and so influences the observed spectrum of malformations that are commonly detected.

4.1 Preimplantation Development

Development in most mammalian species, including humans, is similar through the stage of germ layer differentiation, or during the first one to two weeks after fertilization. As indicated in Figure 4.1, this is often referred to as the preimplantation period; the process is referred to as blastogenesis. These earliest phases of development are marked by a high mitotic activity of pluripotent

Table 4.2—*Chronologies (days of gestation) for selected indices of prenatal development in human and experimental animal species.*

Index Event or Process	Gestational Age (days postconception) ^a					
	Human	Monkey (rhesus)	Rat (outbred)	Mouse (outbred)	Hamster	Guinea Pig
Implantation	8	9	7	6	5	7
Neural plate formation	19	20	9	8	8	13
Yolk sac hematopoiesis	19-63		9-13	7-15		13-35
First heart beat	22		10		8	
Thyroid primordium appears	27		10	9		17
Upper limb bud	28	26	11	10	10	17
Lung bud	28		12	10	9	18
Lower limb bud	29	27	11	11	10	19
Liver appears	30		11			16
Gut herniates	34		13	12		24
Ossification begins	42		16	13	12	25
Hepatic hematopoiesis	42-200		11-22			20
Gonadal differentiation begins	43		14		12	26
Eye lids closed	57	53	18	16	13	
Palate closure complete	57	45	17	15	12	
Gut herniation reduced	60		18	16		
Marrow hematopoiesis	74		17	16		
Thyroid function begins	77		16	15		

^aTypical or approximate times were derived from various texts and compendia and no entry was made when a reasonable value could not be estimated.

cells, during which the fertilized ovum divides into the two-, four-, eight-cell stages, then into a spherical structure, referred to as a morula, while it is still in the oviduct. Upon arrival in the uterus, the growing cluster of cells, now called a blastocyst, lodges in the mucus-covered wall of the uterus and invades the cellular lining or endometrium (uterine mucosa) (Figure 4.2). The blastocyst is composed of the cells that will develop into the embryo as well as other cell populations that give rise to the supporting systems for the embryo/fetus.

The cells of the embryo proper are surrounded by a continuous protective cellular layer that is in direct contact with the maternal cells. From this time and throughout the remainder of gestation, in many respects the embryo/fetus is parasitic—deriving nutrition from and returning waste products to the maternal circulation. Over the next five months, the protective cellular layer develops into a complex structure that maintains the interface between the woman and her fetus throughout gestation. This structure, which becomes the placenta, forms a barrier between the two distinctly separate individuals. The placenta is the major site of maternal-fetal nutrient and waste product exchange, provides an immunological barrier to avoid rejection, and produces biological molecules needed by the embryo/fetus. This structure develops and changes significantly throughout gestation, responding to the changing fetal demands, finally being sloughed with the birth of the baby. The development of the placenta and its role in the exchange of materials to and from the embryo/fetus are described in later sections.

4.2 Implantation and Early Post-Implantation Development

The period following implantation is characterized by development of three primitive germ layers that will constitute the embryo and its extraembryonic structures. These processes are followed by the organization of cells of the layers into the primordial organ systems of the early embryo. Collectively, these stages are referred to as organogenesis, or the period of organ formation.

4.2.1 *Embryo*

The blastocyst, resulting from division of the fertilized egg, enters the uterus approximately 5 d after fertilization. At this stage,

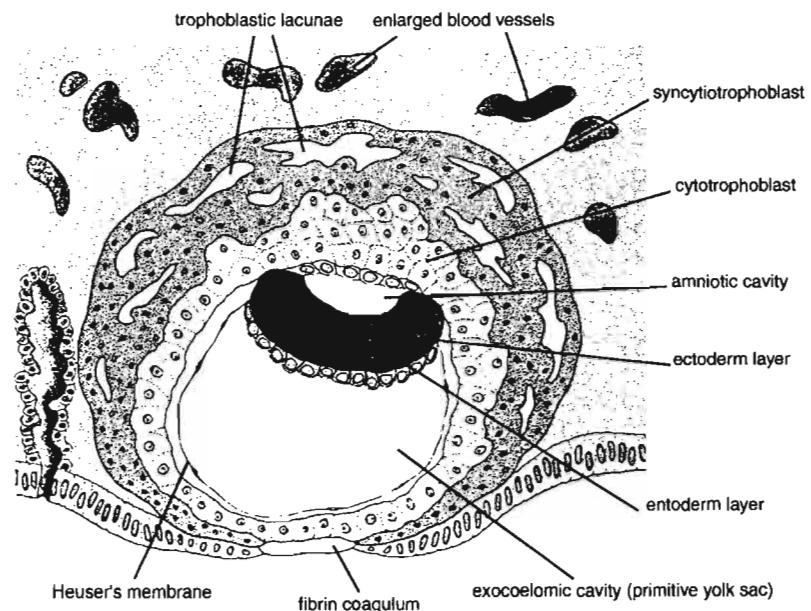


Fig. 4.2. Cross-sectional drawing through the endometrium showing an early implanted human embryo (about 9 d). The mesoderm has not yet developed, but the ectoderm and endoderm layers of the primitive embryo are visible along with the layers of the surrounding trophoblast (from Langman, 1974).

it consists of two layers of germ cells, the ectoderm and endoderm, and is surrounded by a shell of trophoblastic cells, which forms a protective cavity around the germ cells. The blastocyst implants by eroding the maternal tissue and embedding into the epithelial lining of the uterus. Disintegration of small uterine blood vessels and necrotic tissue leads to formation of sinus-like spaces into which maternal blood collects. The resultant hemorrhage and necrosis of the maternal cells, combined with the phagocytic ability of the trophoblast, constitutes the source of nourishment for the embryonic cells during early development.

The specific morphogenetic effect brought about by a chemical stimulus that is transmitted from one embryonic part to another is known as induction. This is considered to be the primary and widespread mechanism by which tissues or organs are directed to form from nonspecific or pluripotent cells or to assemble as composites from different cell sources. Extensive inductive processes take

place during the earliest phases of organogenesis and a third layer, mesoderm, subsequently migrates between the two initial layers, both in the embryo proper and the extraembryonic structures. During early organogenesis, the mesoderm begins to progressively segment into a series of paired masses referred to as somites. This process begins at the head at 21 dg (day of gestation), which is the same time the neural plate begins to fold (Altman and Dittmer, 1962). Interactions among the three layers lead to the characteristic microscopic morphology and function of the embryo and its supporting structures.

These interactions lead to the formation of the structures that define the earliest body axis, including the primordial CNS, circulatory system, and gut, and are responsible for development of the external characteristics. These processes are followed by differentiation into specific organs and organ systems, which is the most characteristic phenomenon of organogenesis. Cell death, mitotic delay and defects in cell migration are the major causes of morphologic lesions or malformations. Genomic changes during this period or earlier may lead to cell death and alterations of the induction process (Wilson, 1973).

The proliferation of these primordial organs, including the CNS, is accompanied by continuing remodeling processes. In a segmental manner, the initial neural plate forms into the neural tube and is followed by outpouchings that result in the primitive brain and nervous system. An analogous series of dilatations, coalescences and ramifications form the heart and other portions of the circulatory system while yet other invaginations and outpouchings give rise to the gastrointestinal (GI) tract and its important derivatives. During this period, the mesoderm organizes into somites to form the axial musculoskeletal system and there is lateral growth of mesoderm/ectoderm to form the limbs with concomitant growth of nerves and vessels into these structures as well as into visceral structures.

4.2.2 *Extraembryonic Structures*

At this early stage, nutrients are stored in and absorbed through the primitive yolk sac, which is in direct contact with the ectoderm layer of the germ and hematopoietic cells. The yolk sac soon changes into the secondary yolk sac from which the mucous membranes of the intestine develop. Though its role in nutrition is less important in human development than in rodents, the

secondary yolk sac is still detectable by ultrasonography after the fourth month (Mantoni and Pedersen, 1979; Sauerbrei *et al.*, 1980).

From 13 to 20 d, the trophoblastic layer differentiates into two cell layers. The outer layer, the syncytium, forms a border around the embryo and is in direct contact with the maternal tissue.

The inner layer, the cytotrophoblast, continues to expand, forming bulges or villi, which dip into the fluid-filled spaces caused by the disruption of the maternal tissue. The embryonic blood vessels develop within the villi. Eventually all the villi are linked to the primitive circulatory system of the fetus through the allantoic vessels in the embryonic body stalk with circulation beginning by 21 d.

The villi initially cover the chorion, which is the absorptive membrane that surrounds the fetus. As the fetus enlarges into the uterine cavity, however, the villi recede to become limited to the region of attachment to the uterine wall, where they become more numerous and grow longer, thicker stems.

4.3 Fetal Period

4.3.1 *Fetus*

Later gestation is referred to as the fetal period (Figure 4.1); its relative length differs among species. The fetal period may occupy from less than one-third of the prenatal period in rodents to more than two-thirds in primates. This phase of development is characterized by growth and by histogenesis, the processes by which organs and tissues progress from primordial structures into the more highly differentiated microscopic states that are present at birth.

4.3.2 *Placenta and Extraembryonic Structures*

By the third and fourth months of human gestation, the sinus spaces have developed into primitive placental cotyledons; chambers where the spiral arteries of the uterus spurt blood into open spaces surrounded by fetal villi. The villi are bathed by maternal arterial blood which passes over the villi and back into venous collecting vessels; this is the transfer site between maternal and fetal circulations (Figure 4.3).

During the last four months of pregnancy the mature placenta is lobular in nature, consisting of the fetal cotyledons. The intervillous

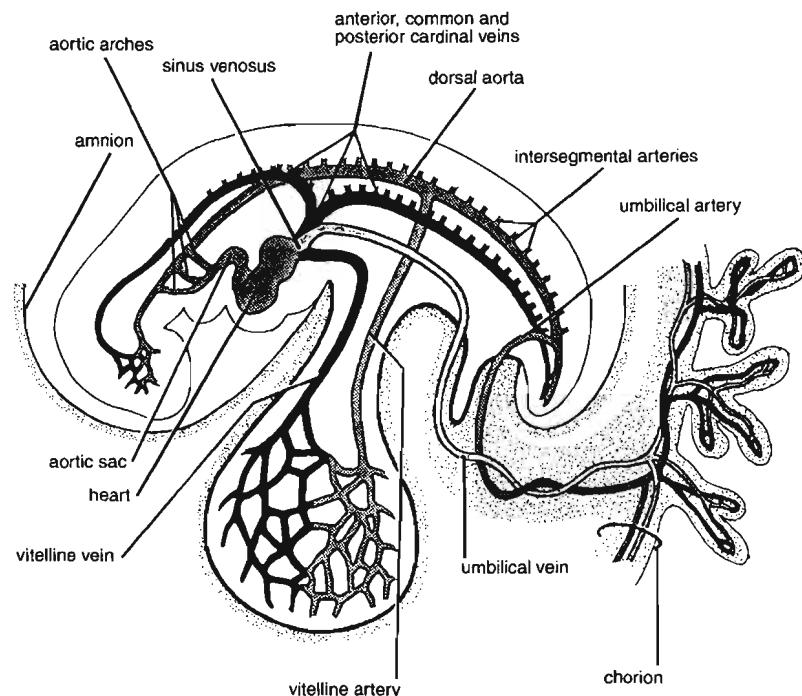


Fig. 4.3. Drawing of the primitive cardiovascular system of a 26 d human embryo (~2 mm crown-rump length) illustrating the flow of blood to and from the vascular plexus on the yolk sac through the vitelline arteries and veins (left side only). The umbilical arteries carry deoxygenated blood and waste products to the chorion (embryonic part of the early placenta) for transfer to the maternal blood, and the umbilical vein returns oxygenated blood and nutrients (from Moore, 1988).

spaces within the cotyledon become smaller as the surface area of the villi increases. This is accomplished by an increase in the number of villi and an increase in the diameter of the fetal capillaries in each villus. Concurrently, the thickness of the barrier membrane between the maternal and fetal blood decreases from approximately 0.025 mm in the first trimester to approximately 0.002 mm or less at term, which facilitates bidirectional transport of materials (Ramsey, 1982; Wegst and Davis, 1992).

Transport is also aided by the flow pattern between the maternal and fetal blood (Figure 4.4). Because initially the maternal blood in the cotyledons flows from the spiral arteries to the fetal side or chorionic plate and the fetal blood enters from the chorionic

plate and flows toward the spiral arteries, a counterflow pattern results. This maximizes the concentration gradient so that substances pass more readily from one system to the other (Battaglia and Meschia, 1986).

The mass of the human placenta relative to that of the fetus varies with gestation age (Wynn, 1968). At three months, the fetus weighs approximately 10 g and the placenta weighs 20 g or more; by the next month, the weight of each reaches 100 g (Figure 4.5). Thereafter, however, the fetal weight increases by a factor of 20 with only a two- to three-fold increase in the weight of the placenta. Therefore, with little increase in mass, increased efficiency permits a great increase in the amount of material supplied to and removed from the fetus. The differences between the growth patterns of the crown-rump length and mass have implications for calculations of radiation absorbed dose (see Section 5.5 and Section 7.2).

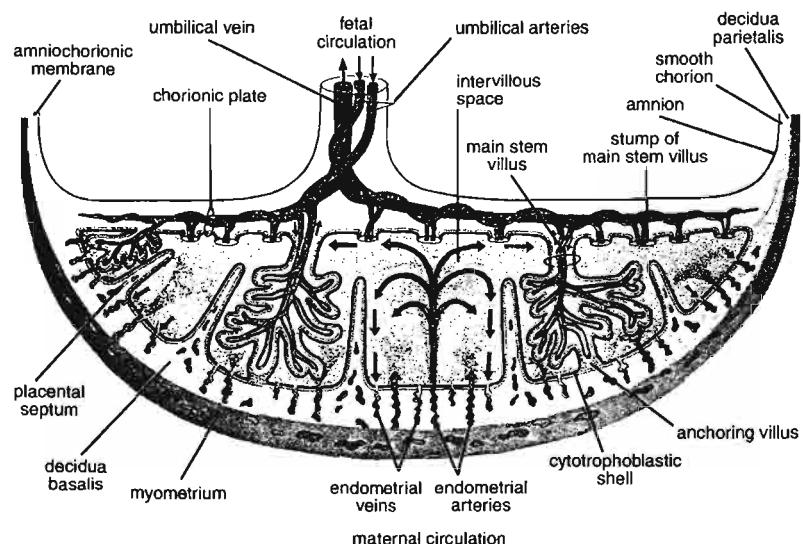


Fig. 4.4. Diagrammatic section through a mature human placenta showing the relation of the villous chorion (fetal placenta) to the decidua basalis (maternal placenta). Blood arrives from the fetus through the umbilical arteries which flow into main stem villi that branch into the villous structures. Spurts of maternal blood are driven into the intervillous spaces and exchanges occur with the fetal blood as the maternal blood flows around the villi (from Moore, 1988).

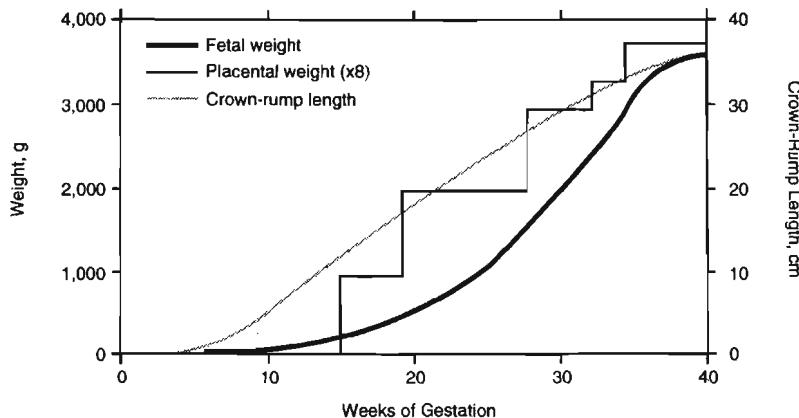


Fig. 4.5. Weight and crown-rump length of human embryo/fetus as a function of gestational age, expressed in weeks after fertilization. Values are a composite of values for a well-nourished conceptus, as synthesized from various compendia. The data of Wynn (1968), which were reported for several-week periods during later gestation, are given as a stepped line that is superimposed onto these graphs.

4.3.3 Comparative Placental Morphology

All mammals, with the exception of marsupials and monotremes, nourish their embryos and fetuses through a placenta. Among mammals, there are a wide variety of placental shapes. However, there appear to be smaller differences among the fetal membranes than among the appearances of the adults (Mossman, 1987; Wegst and Davis, 1992). This may be due to the absence of external environmental changes causing pressure for adaptation. The placentas of primates such as apes and humans are strikingly similar, as are the placentas of the dog and sea lion, both of the order Carnivora. The shape of the human placenta and that of other primates resembles a single disc, hence the descriptive name, discoid. Rodents have a similarly shaped placenta. In sheep, however, the cotyledons form separate entities, appearing like buttons sewn onto the uterine lining. As they do not erode into the uterine lining, they can be sloughed with little maternal bleeding.

Just as their shapes are different, the morphology of placentas also varies among orders. An attempt was made by Grosser (1933) to classify the various types of chorioallantoic placentas relative to the intervening fetal-maternal tissues. For example, in the pig, the placental chorion lies directly opposed to the maternal epithelium

as no erosion of the maternal tissues takes place. Placentas of this type are classified as epithelio-chorial and represent the least destruction of the maternal tissues and the greatest number of cellular layers through which the transport of materials must occur.

There are three layers of maternal tissue; vascular endothelium, connective tissue, and epithelium—and three layers of fetal tissue; trophoblast, connective tissue, and endothelium. The human placenta, in which there is complete destruction of maternal tissue leaving the maternal blood in direct contact with the fetal villi is categorized as hemo-chorial composed of a layer of trophoblast, connective tissue, and endothelium. The status of villi are the basis for Grosser's classifications, as modified by Mossman (1987). This concept is still generally applicable, although electron microscopy has revealed thin structures that were not resolved by light microscopy.

The function of the placenta will be considered in Sections 5 and 7. Many substances diffuse with relative ease through several membranes. It should be noted, however, that the rate of transfer and the net quantity transferred does not necessarily correlate with the number of membranes between maternal and fetal blood supplies (Faber and Thornburg, 1983; Ramsey, 1982).

4.4 Fetal Organ Systems

Details of the development of fetal organs and organ systems are provided in standard textbooks of anatomy and embryology. The following abbreviated descriptions are provided for those systems that have special relevance to consideration of internal radionuclide dosimetry and effects.

4.4.1 *Central Nervous System*

The developmental patterns of cerebral cortex and other brain regions are generally similar in humans and most other mammalian species. CNS development continues throughout the fetal and neonatal periods. Its development involves complex interactions between migration of primordial cell populations, their proliferation, and differentiation into intricately interconnected neuronal processes.

The nomenclature used for components of the prenatal brain has evolved through the years as ontogenetic relationships to adult structure became more clear. The structure of the embryonic brain

may be approximated by considering that it involves several indistinct layers that evolve from the neural tube. In order from the outer surface to the ventricles or lumen, they are: marginal zone, cortical plate, intermediate zone or subcortical plate, synthesis zone, and subventricular/ventricular zone. The microscopic appearance of the telencephalic neuroectoderm of later embryos is a pseudostratified columnar epithelium that gives rise to several histologic types.

Histogenesis of the CNS involves a series of processes during which some cells from the intermediate zone of the subcortical plate, where DNA synthesis takes place, migrate to the periventricular zone. The cells undergo mitosis at that site and then migrate back toward the peripheral zones of the brain. One daughter cell remains in the intermediate zone, but the other continues migrating and becomes positioned in the cortical plate. Each generation of cells migrates through those that previously entered the cortical plate and assumes a location closer to the surface; thus, cells closest to the external surface are the most recently formed. It is thought that the migration pathways are associated with the formation of neuronal processes or fibers from glial cell migration; this phenomenon is under hypothalamic control and operates *via* a form of contact guidance. Cells that are determined to migrate in specific directions also accumulate in discrete zones, which leads to the characteristic layering of the brain as development progresses, and to establishing synaptic connections.

4.4.2 Circulation

Both blood vessels and blood cells are derived from mesenchyme. The preliminary phases involve blood islands of the yolk sac that give rise to erythrocytic series, endothelium and fixed mesenchymal cells, and subsequent "fixed" connective tissue cells that are often considered to be the primary blood forming tissue. Within a few days, primitive angioblasts appear to spread through the body stalk and yolk sac to form blood islands and the flattened endothelia that expand in distribution and coalesce to form vascular spaces.

Differentiation of the vasculature tends to be precocious in mammals, possibly as a correlate of the absence of yolk, and proceeds through networks of capillary plexuses that form into arterial and venous trunks. The mesenchyme adjacent to these capillary plexuses is induced to form the muscle and connective tissue layers of arteries and veins. The vascular pattern is

characterized by a tendency toward pairing; this accompanies the formation of somites, the differentiating segmental condensations of mesenchyme. The paired vessels begin to form a series of connections that pass through the aortic arches. At about the 12 somite stage (3.5 weeks), the component halves form a single heart, which is then followed by fusion of the two dorsal aortas into a single descending aorta. There are several complex processes and interactions, details of which will not be presented here, that take place to form the heart and the subsequent vascularization. Concomitant with somite formation, the primary vessels give off branches that form the umbilical and vitelline vessels. These vessels pass through the body stalk to form the placental connections that provide communication between the blood supplies of the embryo/fetus and the woman.

4.4.3 *Blood-Brain Barrier*

The inclusive expression, blood-brain barrier, is used to describe a number of mechanisms that prevent and control the exchange of materials between the blood and the brain or cerebrospinal fluid (CSF). It also is used to refer either to anatomical structures that serve to exclude passage of substances or to the metabolic activity of cerebral endothelial cells that remove materials by active transport.

There are three anatomical sites of the barrier in adults. The cerebral endothelial cells exhibit tight junctions that prevent between-cell passage from the blood to the brain. Also, tight junctions between the epithelial cells of the choroid plexus prevent passage of protein between the blood and CSF. In addition, tight junctions exist at the pia-arachnoid surface.

In the fetus, a fourth site is believed to exist across the neuroependyma, which lines the inner surface of the developing brain vesicles, preventing passage of protein from the CSF to the brain. Ultrastructural studies in sheep embryos at ages from 20 d to term have shown that well-formed tight junctions are present in cerebral endothelium, choroid plexus epithelium, and the pial-arachnoid membranes at very early stages of embryonic development. In fact, as soon as choroid plexus epithelial or cerebral endothelial cells differentiate, they are found to create well-formed tight junctions (Rapoport, 1976).

Nevertheless, molecules such as sucrose and insulin penetrate into the brain of immature animals more readily than in mature animals. It has been found that the barrier to albumin matures

more rapidly than that of bilirubin (Lee *et al.*, 1989) and that maternal and isogeneic immunoglobulins penetrate completely into all parts of the neuraxis of the neonatal rat (Hulsebosch and Fabian, 1989). The greater ability to transfer from the blood to the CSF of the immature brain is believed to be related in part to the proportionately greater surface area for exchange, as well as to the slower secretion rate of CSF in the immature brain. There may also be a transcellular route between the blood and CSF in the choroid plexus for proteins and lipid-insoluble molecules (Adinolfi, 1985; Saunders and Møllgård, 1984).

Various anatomical and functional aspects of the blood-brain barrier begin to develop at an early fetal age. There is transport of some large molecules into the fetal brain due to physiologic needs and to the metabolic requirements of the growing tissue (Cornford and Cornford, 1986). Experimental studies of radionuclide distribution in pregnant animals infrequently analyzed tissue from the fetal CNS. Published data are not available to determine which radionuclides of interest may penetrate into fetal brain, but the blood-brain barrier would not apply to ionic species or to relatively simple metabolic compounds.

4.4.4 *Thyroid*

The human thyroid gland develops from a medial endodermal thickening that is considered as the primordium of the median thyroid as early as 30 dg (Altman and Dittmer, 1962; Langman, 1974). The developing thyroid does not accompany elongation of the embryo so that it appears to descend. By seven weeks, it is in its final site in front of the trachea, and consists of two connected lobes. By 10 weeks, cellular foci have differentiated into the so-called follicles that consist of single layers of cells surrounding lumens that begin to fill with colloid. At this stage, the gland has an intrinsic capability to concentrate iodine and begins to synthesize thyroxine (Shepard, 1967; Sugiyama, 1971). Thyroid hormone synthesis begins at 10 weeks and increases through week 12, coincident with development of the anterior pituitary and its secretion of thyroid stimulating hormone (TSH). Levels of TSH remain low until 18 weeks, but a rapid increase occurs at 18 to 24 weeks resulting in histologic maturation as well as an increase in the iodine uptake by the fetal thyroid (Barnes, 1968; MacNaughten, 1969). The fetal TSH levels remain high until term, and the fetal thyroid remains hyperactive throughout the third trimester producing free thyroxin (T4) levels that may exceed the maternal levels. Levels of

triiodothyronine (T₃), however, remain relatively low. The levels begin to change abruptly at birth and reach adult values by one week of age.

There appears to be no barrier to the exchange of inorganic iodine between mother and fetus. There is little correlation between the maternal and fetal concentration of organically-bound iodine in blood, which suggests that there is little or no transfer of hormonal iodine (MacNaughten, 1969).

4.4.5 *Bone*

During differentiation, the somites give rise to the musculature, fibroblastic precursors of the connective tissues, and the chondroblasts and osteoblasts that are involved with the formation of cartilage and bone, respectively. Because of differences in formation and architecture, the skeletal system is often considered to consist of three portions: (1) skull, which is composed of the neurocranium (brain case) that develops through membranous ossification of flat bones and chondrocranium (base of skull), (2) appendicular skeleton that is formed by endochondral ossification, and (3) the vertebral column.

The flat bones are formed by a layering of the mesenchymal cells. Some cells differentiate into bone-forming osteoblasts and deposit matrix and intercellular substances resulting in prebone or osteoid (Langman, 1974; Moore, 1988). Calcium phosphate is deposited in the osteoid as it is transformed into the bone matrix that subsequently calcifies from ossification centers. Dense mesenchyme subsequently forms periosteum, which invests the prebone, and the inner periosteal cells differentiate into osteoblasts that deposit parallel plates of compact bone.

The appendicular skeleton develops from limb buds that become visible as paddle-shaped protrusions by five weeks of gestation. Initially the limb buds consist of a mesenchymal core that is covered by ectoderm. Apoptosis (programmed cell death) leads to distal separations of the mesenchyme that give rise to formation of digits and other individual elements (Kerr and Searle, 1980). Interactions between these cell types during remodeling leads to development of cartilaginous models of the bones. These soon become covered by periosteum. Subsequently, there is invasion of vascular buds and differentiation of osteoblasts and osteoclasts that are primarily involved in the calcification and remodeling of the developing bone.

Analogous processes are involved in formation of the vertebral column, which begins with migration of the sclerotomes of the

somites so that they surround the spinal cord and notochord. Chondrification centers begin to appear in the mesenchymal vertebrae at six weeks of gestation and continue through the seventh week. Ossification centers fuse to form the vertebral arches; primary ossification centers of the arches are evident at seven weeks and the process continues through 12 weeks of gestation.

Biochemical changes and mineral deposition are corollaries to the morphologic development. The concentrations and amounts of phosphate in the forming prebone and bone and in the developing skeleton progressively increase through gestation (Widdowson, 1968). Calcium deposition is an intrinsic component of the ossification and calcification processes and the concentration in the skeleton and its components, as well as total content, progressively increase through gestation.

4.4.6 *Yolk Sac Derivatives*

Cells from blood islands of the yolk sac subsequently migrate into the post-implantation embryo (Barnes, 1968). These are the progenitor cells of the gametes and they also give rise to the initial hematopoietic cell lines of the embryo. Death or reproductive cessation of these cells may occur, and there is evidence that they are susceptible to latent effects that can be expressed as toxic changes in subsequent cell lineages.

The progenitors of the gonads appear in the four-week embryo as a pair of longitudinal genital or gonadal ridges. During the sixth week, primitive gametic cells, which originate in the yolk sac wall, migrate along the dorsal mesentery of the hindgut to invade the underlying mesenchyme of the ridges and become incorporated in the primary sex cords. They provide the initial parenchymal cell population that acts to induce gender-dependent differentiation, *i.e.*, toward ovary or testis as well as becoming the reproductively relevant population.

The initial circulatory pattern of the early embryo is such that umbilical veins connect with the placenta and provide oxygenated blood. The vitelline vessels that produce the circulation from the yolk sac are little involved with transport of oxygen or nutrients except for brief species-dependent periods. These vessels provide the initial embryonic source of vascularization in the liver, in which the next wave of embryo/fetal hematopoietic function begins at about six weeks of gestation.

5. Maternal-Fetal Exchange

5.1 Availability for Transport

Substances cannot reach the embryo/fetus unless they are in the circulating maternal blood. If a pregnant woman ingests a substance, it must be absorbed into her blood stream from her digestive tract before it becomes available to the placental villi. Inhaled materials can enter blood through one of two primary routes. Soluble substances and gases such as oxygen, krypton, xenon, iodine and radon may be directly absorbed through the alveolar capillaries. Other less soluble materials, particularly those that are particulate, may lodge in the lungs and be carried upward to the oral cavity and then swallowed. The materials may be soluble in the acidic media of the stomach and then absorbed into the blood. Substances in contact with the skin may be absorbed through the skin or gain entrance into the blood *via* puncture wounds. Radiopharmaceuticals used for medical purposes may be injected intravenously or intramuscularly using standard protocols for the diagnostic or therapeutic procedure.

Once a material is in the maternal blood, there is a potential for its transfer to the embryo/fetus. It was formerly believed that the placenta acted as a complete barrier to harmful substances, but it is now known that this is incorrect. Most substances that enter the maternal blood can be detected in the fetal blood, with concentrations that range from near zero to the same as the concentration in the maternal blood. A few substances needed for the growth of the fetus, such as iodine, can attain higher concentrations in fetal blood or tissues than in the corresponding maternal tissue. It is usually difficult to predict the exchange pattern for a given substance.

5.2 Mechanisms of Transfer

5.2.1 Simple Diffusion

Simple diffusion is the basic mechanism for transport of substances across a cell or other membrane. It can be described by Fick's Law:

$$\frac{\Delta q}{\Delta t} = -KA \frac{\Delta c}{\Delta x} \quad (5.1)$$

where:

- Δq = quantity of substance transferred
- Δt = time interval
- K = diffusion coefficient
- A = surface area of membrane
- Δc = concentration difference
- Δx = membrane thickness

The force acting on nonelectrolyte solutes being transported is the concentration gradient. The gradient is ultimately controlled by maternal and fetal concentrations in extracellular space, degree of binding to maternal and fetal proteins in plasma and tissue, and excretion or metabolism by the fetus, mother and placenta. For example, if fetal tissue reduces the fetal plasma concentration more rapidly than the maternal plasma concentration is reduced by binding and metabolism, transport will be in the fetal direction. Similarly, if a material is injected intravenously into the woman, her initial plasma concentration will be high and the material will be transported to the fetus. As the maternal concentration decreases by generalized distribution, selective organ uptake, metabolism, or excretion, the direction of net transport may reverse.

For materials with high diffusion coefficients or placental permeabilities, the mechanism limiting their transport is the net flow between the fetal and maternal blood, and transfer of these materials is described as being flow limited. In areas of the placenta where the fetal blood flows in an opposite direction to the maternal blood, exchange of these substances is enhanced. Where membrane permeability is the limiting factor, increasing the effective flow does not influence the exchange. Most drugs fall into an intermediate category, being partially limited by permeability and partially by flow. The permeability for any given substance usually must be empirically determined for the species of interest, because there are not yet adequate generalities for prediction of placental transfer.

Transfer of charged molecules is determined by the presence of an electrical potential as well as the concentration gradient. A potential results when the membrane is permeable to some substances but not to others, resulting in an unequal distribution of charged ions. Further, the presence of specific ion pumps, such as those for Na^+ and K^+ , contribute to unequal charge distribution.

The transport of nonelectrolytes is dependent upon molecular weight and effective particle diameter. Water-soluble drugs with molecular weights of less than 600 g mole⁻¹ readily cross, but those greater than 1,000 g mole⁻¹ do not. In certain species there is evidence of water-filled pores which allow the passage of fairly large polar molecules.

5.2.2 Facilitated Diffusion

Membrane transport of some materials is enhanced by binding of the substance to carrier molecules, which results in greater quantities being transported than would take place by simple diffusion alone. This process, called facilitated diffusion, does not involve the expenditure of energy and does not result in the solute becoming more concentrated inside the cell than outside.

5.2.3 Active Transport

Active transport is responsible for the maintenance of some materials at a higher concentration within the cell than in the surrounding medium. It is highly selective, and specific energy-expending mechanisms exist for each actively transported substance. Control mechanisms are often incorporated into the system. For example, transferrin receptors have been found on the surface of the microvilli of the syncytial trophoblast, and it has been postulated that these receptors are involved with transfer of iron to human placental ferritin. The ferritin in the placenta exists in two states, one in which it is stored and one in which it is transported. This enables release of a controlled supply to the fetus when needed. Other substances that are actively transported include calcium, phosphorus, iodine and amino acids.

5.2.4 Pinocytosis

Pinocytosis is a process that involves formation of vesicles in the cell membrane which engulf globules or macromolecules for incorporation into the cytoplasm. Many of these intact macromolecules are transported to the lysosomes where they are broken down into more basic molecules to be used for synthesis by tissues of the placenta, yolk sac, or the developing embryo. This mechanism accounts for the transport of intact protein, fats, steroids and lipid-soluble vitamins. Globules have been observed in microscopic

studies of syncytium and represent an important pathway for large molecules.

5.2.5 Membrane Rupture

In later gestation, microscopic ruptures of the membranes can result in open pathways between the maternal and fetal blood circulations. This mechanism is believed to explain why small numbers of fetal blood cells can be detected in a high proportion of blood samples from pregnant women late in gestation.

5.3 Research Approaches

5.3.1 Introduction

Determining the amount of a material that enters the human fetus is a difficult task, both from the technical and ethical viewpoints. Placental function varies among mammalian species, and a universal model has not been developed for extrapolating placental transfer data from animals to humans. Experiments in pregnant women currently are difficult or impossible so that the most germane model is the nonhuman primate. Expense, long gestation times, and other experimental limitations restrict such studies, although some have been performed. Only minimal amounts of biological data have been accumulated in any species for many materials of importance for prenatal radiation dosimetry. The data needed for completely determining the radiation dose to the fetus from an internally deposited radionuclide includes time-dependent activity quantitation in the mother, fetus and placenta; moreover, maternal and fetal organ data are required when selective concentration occurs. Such information is needed for different gestational ages, and both acute and chronic exposure conditions should be considered.

5.3.2 Human Subjects

5.3.2.1 Purposeful Exposures. Prior to general awareness in the early 1960s of the sensitivity of the embryo/fetus to radiation effects, pregnant women were included in several experiments to evaluate metabolism and nutritional needs. These include studies, for example, in which radioiron was administered to women at

different gestational ages and quantified before or after birth. Similar studies were performed with radioiodine, both as sodium iodide and as labeled albumin, and with several other radionuclides, perceived at the time to be of no hazard. These studies, though performed 30 y ago, constitute the bulk of the human data available today. Results from these evaluations are included in individual element descriptions in Appendix A.

In rare instances, a radioactive material is administered to a pregnant woman to perform a diagnostic or therapeutic medical procedure. If the procedure involves imaging of the radioactivity to determine its distribution, activity may be detected in the fetus and placenta. Nonquantitative indications of fetal or placental activity have been observed, as in the case of placental accumulation of ^{67}Ga citrate, which confirmed data gathered in animal studies (Newman *et al.*, 1978; Watson *et al.*, 1992).

A case has been reported in which a pregnant woman ingested ^{32}P . The exposure was purposeful, although the circumstances are not defined (NCRP, 1998). Bioassays were performed and the radiation doses to the conceptus were estimated using the biokinetic models presented in Appendix A and the methodology of the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine as presented in Section 8.

5.3.2.2 Accidental Exposures. Accidental exposures of pregnant women to radionuclides have been reported as consequences of a number of incidents. However, in only a few cases have the exposures provided additional biological distribution data. Large numbers of women have been exposed to radionuclides released into the environment from accidents such as those at Windscale and Chernobyl. These incidents resulted in widespread release of iodine fission products, which was of concern because of the potential for high fetal thyroid accumulation and the elevated sensitivity of the thyroid to the effects of radiation. The Chernobyl accident also released large quantities of other fission products which have been detected in people and their food and water supplies.

Atmospheric testing of nuclear weapons in the late 1950s and the early 1960s by the United States, France, China and the former Soviet Union released radionuclides into the atmosphere. These were dispersed worldwide and some of the longer-lived radionuclides can still be detected. Fetal thyroid glands were analyzed for ^{131}I content and placentas were analyzed for ^{90}Sr and ^{137}Cs content in the late 1960s. These and numerous other evaluations are described in documents by UNSCEAR (1977; 1986).

A number of women have received therapeutic quantities of ^{131}I for treatment of thyrotoxicosis during pregnancy. At present, the routine use of sensitive tests which can detect early pregnancy is recommended prior to the use of therapeutic radioiodine in women of childbearing age (Zanzonico and Becker, 1992). Occupational exposures have occasionally occurred, resulting in fetal exposures, such as ^{226}Ra received by fetuses of the dial painters. Quantitation of fetal exposure has been performed including analyses of maternal and fetal bone and determination of specific activities relative to calcium (Schlenker and Keane, 1987).

The potential for occupational exposure of pregnant women and resulting radiation doses to the conceptus may increase as larger numbers of women enter the work force. Small exposures may occur with unknown frequency but only rarely have attempts been made to quantitate fetal incorporation of radioactive material resulting from occupational exposure.

5.3.2.3 Perfused Placentas. As an approach to circumvent the ethical difficulties encountered with human studies, perfused placentas have been used for study by numerous investigators (Sikov *et al.*, 1992c). The placenta can be obtained at delivery and maintained in a physiologic state at a controlled temperature while perfusing the maternal and/or fetal vessels with isotonic perfusate. Placental transfer rates can be quantified in the maternal-to-fetal direction or vice versa by adding the substance to one side and analyzing for its presence in the other. The advantages of the method are that placentas are readily available, organ preservation techniques are well established, and perfusion can be carried out with realistic and variable concentrations and flow rates. The disadvantages are that the fetal load has been removed and influences of fetal metabolism, binding or excretion into other spaces are not accounted for.

5.3.3 Animal Subjects

5.3.3.1 Choice of Animal as the Model. A wide variety of animal models have been studied, especially laboratory species such as rats, mice and guinea pigs, and proven experimental techniques are available. Other studies have used dogs, pigs, sheep, baboons and other larger mammals. The placental types of many animals and the human are similar, but other obvious differences such as body size, gestation time, and maturity at birth are notable. The

guinea pig may be preferable to the rat because of smaller litter sizes, longer gestation times, and greater maturity at birth. Many physiologic experiments have utilized sheep or goats. As was noted earlier, the nonhuman primate is the animal of choice because of its greater similarity to the human although few data have been obtained using these species.

5.3.3.2 Applicability of Animal Data. Most information about the distribution and retention of materials during pregnancy, including the placental transfer to the fetus, has been obtained from studies in experimental animals. The studies have been performed for many different purposes, not necessarily relevant to dosimetry. Toxicity studies provide fetoplacental concentrations at death. Serial measurements for determining kinetic parameters provide information on concentrations in maternal blood and tissues, placental structures, and the embryo/fetus as a function of time after exposure. Some studies have investigated parameters such as transport mechanisms and factors that affect placental transfer and fetoplacental distribution.

Distribution and retention of radionuclides often differ among animal species which makes the use of animal data difficult and potentially inaccurate. Pregnancy adds further complications such as variations among species in length of gestation, periods at which fetal organs begin to function, and permeability of the placenta. Other factors influencing the applicability of data from animals to humans are metabolic rates and number of offspring (usually monotocous in humans and often polytocous in other mammals). However, for many radionuclide compounds, only animal data are available, and quantitative extrapolation of the data to humans is required. Methods for extrapolating animal data for calculating radiation absorbed doses in humans are discussed in Section 7.4.1, Extrapolation of Animal Data.

Phylogenetic differences in the visceral yolk sac may explain some of the interspecies differences that have been reported and are described in Appendix A. This structure is of interest because, in the human and most other mammalian species, it is the origin of the initial stem cells of the hematopoietic system and of the gametes. The yolk sac is important for absorption of nutrients by the early rodent embryo. Its size increases and absorptive function persists throughout gestation in rodents, in which species it has a high affinity for heavy metals.

The size, persistence and physiological importance of the yolk sac are less prominent in higher mammals, including humans. A

similar affinity for heavy elements, including plutonium, has been demonstrated in nonhuman primate embryos/fetuses. On the other hand, the umbilical cord, which is not usually analyzed in animal experiments, has been found to have high concentrations of some actinides in human abortuses.

5.3.4 *Conditions of Exposure*

Many of the animal studies that provide our primary database used single exposures to measured amounts of radionuclide, and the studies often employed intravenous or subcutaneous routes of administration. Such experiments provide data that would be primarily applicable to certain types of accidental exposures of an individual pregnant woman and, even there, several caveats are applicable. Inasmuch as most potential human accidental and environmental exposures occur through ingestion or inhalation and may involve repeated intakes of low levels of radionuclide, using the animal data requires multiple extrapolations.

In some instances, radioanalyses of human autopsy materials have yielded fetal-to-adult concentration ratios that are greater than would be expected from animal data involving acute exposure (Weiner *et al.*, 1985). Calculations based on other measurements in human materials, however, resulted in concentration ratios more similar to those seen in animal studies (Prosser *et al.*, 1994). Explanations for differences include several hypothetical considerations and may be attributable to the interaction of several factors, including analytical procedures. Possible reasons include mass effects, summation of the contributions of different time periods available for post-exposure excretion, and kinetic and deposition differences relating to the metabolically different stages of gestation during the successive intakes.

5.4 Exchangeable and Nonexchangeable Substances

5.4.1 *Nutrients—Elemental and Molecular*

Most nutrients and substances needed by the fetus for growth readily cross the placenta, often by active transport mechanisms. Examples include iron, calcium, iodine, sodium and potassium ions. The biokinetics of the radioactive isotopes of an element are assumed to be the same as those of the stable form. The amount of

the substance transported often tends to be related to fetal demands. For example, the greatest quantities of calcium are transferred when the fetal bones and teeth are calcifying, near the end of pregnancy. Significant quantities of iodine cross only after 10 weeks, when the fetal thyroid starts to accumulate iodine and synthesize hormones. Chemical analogues of nutrients (such as strontium for calcium) or compounds of similar size and charge (such as pertechnetate for iodide) may display similar characteristics of transfer to the fetus although they may not be metabolized as readily.

5.4.2 Biological Molecules

The survival of the embryo/fetus depends upon an adequate supply of certain products (hormones and enzymes) produced by maternal organs and the placenta. Thus, many biological molecules are transferred across the placenta *via* specific pathways and many are effectively excluded. Protein hormones do not cross to the fetus in large amounts. Unconjugated steroid hormones, testosterone and progestins cross easily. Maternal antibodies cross the placenta and confer passive immunity to the fetus and newborn infant. Alpha and beta globulins do not reach the fetus, but some gamma globulins do.

Suggestive evidence indicates that viruses associated with smallpox, chicken pox, measles, rubella, encephalitis and poliomyelitis sometimes pass to the fetus and may produce infection or adverse effects. This behavior suggests a potential for a similar transfer of small colloidal forms of some radionuclides.

5.4.3 Radiopharmaceuticals

The radiation dose to the embryo/fetus from a radiopharmaceutical is dependent upon the physical characteristics of the radionuclide and the chemical form and route by which it is administered. These considerations are discussed in detail in other sections of this Report as well as in Appendix A. As one set of examples, technetium-labeled compounds such as pertechnetate and diethylenetriaminepentaacetic acid (DTPA) readily cross to the fetus. The resultant cumulative depositions in the fetus differ because of different rate constants. On the other hand, the placenta is poorly permeable to colloids so that technetium-labeled materials such as sulphur colloid do not cross to the fetus.

Iodide crosses the placenta readily and may concentrate in the fetal thyroid to a higher degree than in the maternal thyroid after the 10th week of gestation. Iodinated compounds or their metabolites may or may not cross to the fetus. Thallium citrate has been shown to cross the placenta of guinea pigs and to reach higher concentrations in the fetal than in the maternal ovary. Thallium has a longer biological halftime in the fetus than in the mother. Only a small fraction of gallium as the citrate crosses to the conceptus, but the placenta binds large quantities. In studies of laboratory animals, as much as 80 percent of the injected gallium has been found in the placenta.

5.4.4 Environmental Pollutants

Several radionuclides, including ^3H , ^{90}Sr , ^{131}I , ^{133}Xe and ^{137}Cs , as well as uranium and transuranic radionuclides, may be present as environmental pollutants. In each instance, the elemental and family characteristics would apply. Many of the elements may be found in any of several chemical forms, which will affect their biokinetic characteristics. Accordingly, transport to the fetus cannot be generalized completely.

5.5 Distribution in Pregnant Women

5.5.1 Tissue Deposition During Pregnancy

Only rarely is there information about changes in organ uptake or retention of a radionuclide that occurs in a woman's tissues during pregnancy. This distribution is an important determinant of the radiation dose received by the fetus. Organ uptake in the nonpregnant female often is used for dosimetric purposes. If an intake of a long-lived radionuclide occurred before pregnancy, maternal clearance processes may result in the radionuclide being present in her blood and available for transfer to the embryo/fetus.

Differential distribution patterns in the pregnant woman may change with gestational age. If there is a significant fetal demand for an element, such as calcium, less may be available for distribution in maternal tissues. Metabolic changes that occur during pregnancy may affect distribution, especially if they are hormonally influenced. It has been shown in laboratory animals, although not documented for humans, that materials such as $^{99\text{m}}\text{Tc}$ pertechnetate and ^{67}Ga citrate may have significantly different organ uptake

patterns during pregnancy (Wegst, 1992; Wegst *et al.*, 1983). As noted previously, a high placental content does not necessarily mean a high fetal content, and, in fact, placental binding may limit transfer of the material.

5.5.2 *Maternal Organs and Placenta as External Sources of Fetal Exposure*

For radionuclides that emit penetrating radiation, the maternal organs may be source organs for exposure of fetal tissues, so the fetus would receive a radiation dose even if no transfer occurred. The maternal bladder contents can contribute to dose for nuclides that are excreted *via* the kidneys, and urinary void time can be a significant factor in calculating the radiation dose to the fetus. The contribution of each organ to the fetal radiation absorbed dose is a complex function of the time-dependent radionuclide content in the organ and the time-dependent spatial relations that define the transport of radiation between the source and target regions as well as the decay properties of the radionuclide.

The placenta can be a source organ for radiation exposures of the fetus. There is selective placental localization of some materials, such as gallium, but little transfer to the fetus. Such localization, however, can lead to placental and fetal irradiation if penetrating radiation is emitted. As discussed in Section 4.3, the relative sizes and geometries of the placenta and the fetus change during pregnancy. At approximately 20 weeks, the placenta partially surrounds the fetus but placental dimensions are small compared to the fetus towards the time of birth so that only a small part of the fetus would be directly apposed to the placenta. Therefore, the fraction of photons emitted by radionuclides in the placenta and absorbed by the fetus is a function of gestational age and fetal position.

6. Effects of Prenatal Irradiation

The physical mechanisms that produce effects from internally-deposited radioactive materials do not differ from those that pertain to irradiation by external sources. Accordingly, this Section will first present underlying generalities about stage-dependent radiation effects on prenatal development and its postnatal sequelae. Most of the results have been determined from experiments that used acute exposure of mice and rats to uniform fields of x or gamma rays at relatively high-dose rates. These patterns, which are generally summarized in Figure 6.1, are only roughly applicable to other conditions of exposure.

It is convenient to categorize effects as early, delayed and late, based on their nature as well as time of detectability. The responses of the embryo and early fetus to irradiation are similar in human, nonhuman primate, and lower mammalian species, and reflect similarity in developmental patterns as modified by differences in absolute durations of individual stages. Characteristics specific to the species become more prominent later in gestation, and the differences in maturity at birth are associated with differences in response and apparent sensitivity.

The several distinctions become less clear with protracted exposures. The spectrum of effects within each category often shifts with radionuclide exposures where there may be both protraction and inhomogeneous distribution of the radiation dose. Special features of effects associated with exposures to internally deposited radionuclides are discussed in Section 6.5.

6.1 Early Effects

Early effects are those that arise from alterations of cells present at the time of irradiation or the first several generations of their progeny. Sufficiently severe alterations can lead to mitotic inhibition, cell death, and interruption of the pregnancy. Depending on time of exposure and species, early prenatal deaths may be

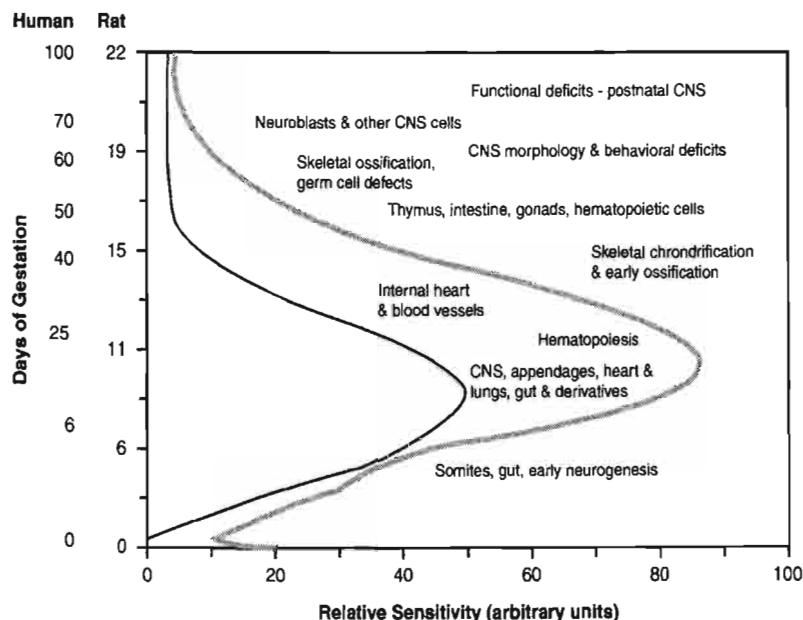


Fig. 6.1. Generalized representation of gestational-age-related sensitivities to radiation-induced developmental effects in the human and rat embryo/fetus. Curves illustrate relative sensitivities for lethality (—) and for abnormalities of structure or function (---). The indicated lesions and systems or organs are those characteristically affected at successive developmental stages (modified from Rugh, 1969).

displayed as reduced fertility, miscarriage or abortion, or as decreased litter size or increased resorption in rodents. Early defects of the inductive processes, which lead to later malformations of the surviving embryos, also may be detected as alterations of metabolism or physiology.

6.1.1 Preimplantation Period (*Blastogenesis*)

The earliest phases of development involve pluripotent cells with high mitotic activity, which evolve into the blastocyst that implants into the uterine mucosa. The lowest dose that produces detectable inactivation of individual blastomeres is about 0.05 Gy of acute x irradiation for mouse embryos *in vitro*. Despite the radio-sensitivity of individual cells, the preimplantation period is characterized by a high capacity for regeneration and reorganization, so

that studies of rodents exposed during blastogenesis usually do not provide indications of persistent effects.

Effects of preimplantation irradiation are characterized by a moderate sensitivity for killing of the murine morula and effects of acute exposure can be detected at approximately 0.1 Gy.

Estimates of the incidence of spontaneous miscarriages in the human population range from approximately 30 to 50 percent, so exposure of women at early stages could lead to undetected embryonic deaths. There is an all-or-none response over a wide range of doses (Brent, 1980b). Preimplantation or early post-implantation deaths may occur or there may be complete restitution; accordingly, the survivors usually develop into fetuses that have normal morphology. The literature does not contain clear-cut indications of other types of effects from exposure during this period.

6.1.2 *Period of Organ Formation (Organogenesis)*

Cell death and mitotic delay during organogenesis can lead to defects in the induction process and traditionally have been considered as the major cause of morphologic lesions or malformations (Brent, 1994; Streffer and Molls, 1987). Proliferation is accompanied by remodeling: the neural plate forms into the neural tube and outpouchings result in the primitive brain, the complex structure of the heart is attained, and external body form is developed, ranging from limb shape to facial features. Extensive intrauterine selection, especially in the human, often precludes further prenatal development of embryos that have major defects. In rodent experiments, because of balance between selection and embryonic capacity for regeneration and reorganization, some survivors in exposure groups, or even within litters, may be normal while others are malformed.

Production of malformations is the characteristic effect of irradiation during the period of major organ formation, and involves concepts and chronologies for times of special radiosensitivity during organ differentiation (Brent *et al.*, 1987; Konermann, 1987; Sikov, 1992c). Typically, experiments in rodents have yielded sigmoidal dose-response curves for external malformations and skeletal defects, and no-effect levels or practical thresholds are sometimes detectable. In general, the threshold for teratogenesis during the early or main inductive phase appears to be lower (about 0.05 to 0.1 Gy) than during major organogenesis (threshold range 0.15 to 0.25 Gy). Sensitivity to embryolethality is also reduced during major organogenesis, and the potential for selection

concurrently decreases. Although insufficient data exist to construct unequivocal dose-response curves for teratogenesis specific to the human embryo, there are no reasons to believe that the foregoing threshold ranges are not generally applicable.

There have been numerous descriptions of malformed abortuses or congenitally malformed children after radiotherapeutic exposures during pregnancy (Dekaban, 1968). In most of these cases, stages of gestation could only be estimated, but the exposures were fractionated over periods of several weeks. Although the precise doses were not known, they were in the range of several gray.

Similar uncertainties apply to intrauterine exposures from atomic-bomb detonations in Japan, especially at gestational stages prior to brain corticogenesis. The paucity of gross malformations in this population is considered to indicate selection against intrauterine survival of affected individuals. These various factors, as well as the preponderance of CNS malformations, introduce difficulties in interpretation. Nonetheless, the pattern of malformations observed in humans exposed to radiation during early embryogenesis or during organogenesis is readily reconciled with that seen in experimental animals (Brent, 1994; Brent *et al.*, 1987; Konermann, 1987; Sikov *et al.*, 1992a).

Inconsistent relationships between dose and embryoletality in the lower dose range are suggestive of biological variability in experimental animal populations. Nevertheless, there is often a sharp inflection of the curve that precedes a rise in incidence, especially with fractionation or protraction of the dose. It may be assumed that human populations possess even greater heterogeneity and variability, which would have consequences for radiological protection. Although these complex relationships pose a potential for misleading conclusions, they have not yet received adequate attention in risk analyses.

6.1.3 *Period of the Fetus (Fetogenesis)*

As indicated above, the fetal period is characterized by growth and histogenetic processes by which organs and tissues progress from primordial structures into the more highly differentiated histologic states present at birth. This phase of development is brief in many rodent species, but it is more than two-thirds of the prenatal period in primates. Acute radiation exposures of rats or mice during this period have less effect on intrauterine mortality than during organogenesis, although the incidence of neonatal mortality tends to increase at sufficiently high doses. Decreased

susceptibility to intrauterine lethality from irradiation is evident only in the late fetal stages. Other types of change become of increasing importance during the fetal period, and irradiation tends to produce developmental retardation but has little effect on the basic shape or structure of most organs. Sensitivity at the cellular level remains essentially the same, however, which is of importance in considering formation of specific populations such as germ cells and structures in the CNS.

Irradiation may yield a mosaic of surviving and reproductively dead cells in embryonic or fetal tissues. The nonuniformity of response seems related to differences in sensitivity and repair capacities associated with stage of the cell cycle. Damage to the cell nucleus or chromosomes may lead to acute cell death, chromosomal aberrations, or aneuploidy, as well as inactivation or delayed death of daughter cells. The incidence of cytogenetic effects appears to increase linearly with dose from 0.05 through 0.25 Gy, again depending on stage of gestation, with selection against aneuploid cells and those with micronuclei or other chromosomal aberrations. The cell losses that result from cytogenetic alterations, rather than the defects *per se*, seem to be the determining factor for many developmental effects. However, genetic alterations may be involved in carcinogenesis and other late effects.

As was described, progenitor cells of the gametic and hematopoietic lines form in blood islands of the yolk sac during early organogenesis, and migrate into the embryo. These early cells are susceptible to apoptotic or reproductive death, and to induction of latent effects expressed in subsequent cell lineages. Inactivation has been detected after acute irradiation at times ranging from early primordial cell formation through the fetal period of spermatogonial and oogonial precursors, and the response approximates a linear function over a wide range of doses extending to low doses at the most sensitive stages.

Because the CNS is formed through complex interactions between cell proliferation and migration, interference with either process would affect its development. No special sensitivity to radiation is observed in proliferating cells, including necrosis or reproductive death, during this period. This suggests that the predominance of neural defects during subsequent development is not specifically related to early cell lethality. Nonetheless, there seem to be effects that arise from changes at the cellular level, including reduced cellularity and thickness of brain layers. More commonly, therefore, defects in the lower dose range are believed to

involve the migratory processes and/or subsequent differentiation of the neural cells.

The developmental sequence requires temporal and spatial precision for correct neuronal positioning and synaptogenesis, especially because misplaced cells tend to die. It is considered unlikely that these multicellular events would display a linear dose response or that they would occur following alteration of a single cell. Autoradiographs show relatively little decrease in synthesis in the S zone or cell death in the periventricular zones, while most pyknotic cells are detected in the zones of migration, which contributes to the decreased cellularity and thickness of the cortical plate. Quantification of relative parallelism of nerve fibers shows dose-dependence for each age of exposure, and exposures at later times of gestation are progressively less effective and the threshold dose range increases.

The capacity for compensation of deficits progressively decreases during histogenesis. The potential for restoration is also decreased. Display of damage is increased because it is more likely that affected fetuses will survive than after exposure at earlier stages.

Mammalian species display generally similar teratologic characteristics, including short, stage-specific sensitive periods during early development, and relatively high capacities for restoration. Effects on the CNS may be exacerbated by the progressive loss of neuronal reproductive capacity, which can lead to functional deficits in the absence of gross anatomical brain malformations. As has been noted, scaling is required when relating susceptibilities for specific effects to developmental stage at exposure. Phylogenetic differences also must be considered in comparisons of interactions in humans with those that are important in rodents.

6.2 Delayed Effects

Prenatal irradiation can lead to either overt or latent defects that are displayed as delayed effects or biologically modified expressions of previously-induced defects.

6.2.1 Reduced Organ and Body Growth

Prenatal radiation exposures may result in decreased body or organ weights, with minor stage differences among species. The greatest effects occur with exposure during organogenesis and the

beginning of fetal development. Whole-body radiation doses of about 0.1 to 0.25 Gy produce reductions of prenatal weight in rodents (Brent, 1994). The period of sensitivity for postnatal growth retardation extends throughout the perinatal period of rats and mice. Particularly with exposure during fetogenesis, the effects on the weights of specific organs may be disproportionate to the effect on body weight, so that the weights of unaffected organs, expressed as percent of body weight, may actually be increased. Radiation doses of about 0.25 Gy are required to produce persistent postnatal deficits in body weight of rodents, but absolute and relative decreases in brain weight are detectable with uniform whole-body doses of about 0.1 Gy. Differences in the nature of the response are also related to compensatory proliferation that may occur later in gestation and during the postnatal period.

6.2.2 Structural Defects of the Central Nervous System

A limited number of histopathologic and cytologic examinations of the human CNS following prenatal radiation exposures have been reported. Quite consistently, comparisons indicate that effects of higher radiation doses on neurogenic processes are similar in humans and in experimental animals, particularly those that involve changes in the matrix and cell migration in specialized neural epithelia (ICRP, 1986). There is a programmed succession that leads to qualitatively different cell populations at successive stages; this is probably also involved in the lower capacity of neural tissue to restore lesions. Neuronal cell formation has been mostly completed early in the postnatal period so that subsequent compensation is accomplished through gliosis, which can lead to an imbalance between neural and glial cells.

Observations in experimental animals and humans demonstrate that microcephaly only or cerebral dysmorphology and underdevelopment are the most distinctive and frequent retardation effects. Approximately 0.1 to 0.2 Gy (tissue kerma free-in-air) was the lowest dose range in which significantly reduced head circumference was found in Japanese children from Hiroshima. This effect was not seen below 1.5 Gy in Nagasaki (Blot and Miller, 1973; Plummer, 1952). This also was the dose that seemed to produce children who were both mentally retarded and microcephalic in either city, which is in general agreement with the estimated 2.5 Gy that had been derived from earlier evaluations of clinical case reports in the literature based on radiotherapeutic fractionated regimens (Dekaban, 1968).

6.2.3 *Impaired Neurological Function and Behavior*

The earliest reports of the Atomic Bomb Casualty Commission (ABCC) included observations of mental retardation and retarded physical development in offspring of pregnant women who had been within 2,000 m of the hypocenter, especially those women who displayed radiation sickness or other evidence of effect. The general effects were in accordance with those reported in the early clinical literature (Dekaban, 1968).

The response relationships for these effects relative to dose and developmental stage became more clear as increasingly better estimates of radiation doses became available and subsequent reanalyses were undertaken (Otake and Schull, 1984). The period between 8 and 15 weeks of gestation was the most sensitive time for inducing clinically-determined mental retardation as well as related phenomena including decreased psychometric scores and school performance suggestive of a shift in intelligence quotient (ICRP, 1991b; UNSCEAR, 1988; 1993).

Most affected individuals were in the higher dose range indicated above, with few below 1 Gy. A linear, nonthreshold relation was fitted to the mental retardation data for analytic purposes; this gave a risk factor of 0.4 Gy^{-1} but the confidence interval included "zero dose." Cogent arguments have been advanced that mechanistic considerations suggest that there is a threshold (Brent, 1994; NEA/OECD, 1988a). Further evidence indicates that some of the effect may be secondary to other radiation effects on the woman (Yamazari and Schull, 1990). Although effects are not detectable, the observations and the time interval point out that the developing CNS may be a relevant target organ for dosimetric considerations for radionuclides. The more sensitive time is before the blood-brain barrier has become complete. Radionuclides in ionic form are not affected by the barrier. A less striking effect on mental capabilities was seen in children born to Japanese women exposed in the 16 to 25 week time period, and no increase was detected for other time periods.

Neurological and motor deficits are the most prominent functional alterations in laboratory animals, with a practical threshold dose of about 0.25 Gy for acute irradiation. Such changes may be induced throughout early neurogenesis, but become especially pronounced after exposure during late organogenesis or early fetogenesis, periods that roughly coincide with those during which "latent" structural defects may be induced. Changes in the bioelectric

activity of the brain have been demonstrated, but these are incompletely correlated with the extent of structural damage.

Increased susceptibility of rodents to the induction of audiogenic seizures generally require prenatal exposures of at least 0.25 Gy. The relevance of such nonphysiologic measures cannot be established for humans, and uncertainties about the roles of "emotionality" and motivation make it impossible to assess the significance of reported deficits in learning and behavioral tests performed with rodents. There are difficulties in correlating structure and function, as illustrated by findings that extensive deformation of the visual cortex of the rat did not prevent learning of an optical-motor task. In summary, however, it seems unlikely that doses below 0.15 to 0.25 Gy would affect learning and behavior in rodents, even with exposure during the most sensitive stages.

6.2.4 *Gametes and Hematopoietic Cells*

Based on early cell inactivation, gametogenesis appears to be among the most radiosensitive developmental processes. On the other hand, germ cells have a great capacity for regeneration in the early stages of gametogenesis, as well as a high redundancy and natural elimination rate in adults. Studies with acute and chronic irradiation have shown postnatal fertility to be among the most sensitive indicators of prenatal damage. However, a small cell loss of gametes during development may have no practical implications for establishing radiological protection practices. Clearly, high doses can delay the maturation of specific cell lineages, while the perinatal period seems most sensitive for induction of neoplasms of the hematopoietic system, at least in dogs (Benjamin *et al.*, 1981). Relatively little research has been directed to effects on the postnatal integrity of the hematopoietic system relative to delayed or late effects, especially after prenatal exposure to internally deposited radionuclides, and unanswered questions remain.

6.3 Late Effects

Beyond those discussed earlier, a number of factors preclude making direct quantitative extrapolations from the results of animal experiments to risk estimates for radiation-induced late effects in humans. In many experiments, the animals were selectively bred to have high spontaneous incidences of tumors, leukemia or degenerative diseases so that the predisposition to

developing various lesions in later life may be specific to the stock of animals studied. Several factors such as interactions between differences in life spans, altered endocrine status, competing risk factors in mortality, tumor latencies, and destruction of cells of target tissues are known to be involved in late effects following prenatal irradiation, particularly by external photons, in animal studies. These factors make it prudent to restrict extrapolations to general features rather than to quantitative estimates of risk. Many studies involving exposures at low doses suggest that the effects are obtained *via* tumor promotion and not through induction (Sikov, 1989).

Experimental studies have been performed in a variety of species, but none has provided unequivocal evidence for carcinogenesis or leukemogenesis by irradiation before or during early organogenesis. Oncogenic susceptibility then appears to progressively increase into the neonatal period, and lymphomatous lesions are most frequent after external exposure during the perinatal period. The mammary gland is the site of most increased tumor incidence (UNSCEAR, 1986), although increases have also been observed in the ovary, brain, liver and lung (NAS/NRC, 1990).

The lowest dose of external exposure reported to produce reliable increases in tumor incidence in experimental animals is 0.1 Gy, and doses of 0.5 Gy and above are more commonly found to be the minimum. Some uncertainties about potentially confounding factors remain, but evidence for effects from lower oncogenic doses in humans has been obtained from epidemiologic studies of children who were prenatally exposed during diagnostic radiography. The risk factors in humans for solid tumors and leukemia have been calculated to be 5×10^{-2} Sv⁻¹, for the first 14 y of life (UNSCEAR, 1994) and no stage of gestation was demonstrably most sensitive (NAS/NRC, 1990; Sikov, 1992a; UNSCEAR, 1986).

6.4 Factors Modifying Effects of Prenatal Radiation

6.4.1 Distribution of Dose in Time

Temporal distribution of dose has been shown often to have marked qualitative and quantitative effects on the responses to prenatal irradiation (Brent and Jensch, 1967; Sikov and Lofstrom, 1962). In some infrequent instances using fractionated exposures, synchronization of the mitotic cycles occurred following the first

fraction, which lead to an enhanced response to subsequent fractions. When the exposure is fractionated or protracted, however, the most common finding is a lessening of the incidence or severity of developmental defects. This relationship has been demonstrated for measures ranging from intrauterine survival to fraction of abnormal fetuses. Some of this diminution of effect at lower overall dose rates relates to usual cellular radiobiological repair phenomena, as well as to the greater time available for restorative and compensatory processes to occur. As a corollary, moreover, a major portion of this effect probably derives from the fact that each successive developmental stage receives a smaller dose. These factors must be considered in evaluation and prediction of effects from internal radionuclides in a situation where the radiation dose will be delivered over extended time periods that encompass multiple developmental stages.

6.4.2 Relative Biological Effectiveness and Radiation Weighting Factors

The radionuclides of concern in environmental and occupational exposure emit a wide spectrum of radiation types including alphas, betas, neutrons and photons. Evidence from studies of experimental animals suggests that their relative effectiveness in producing biological damage to the conceptus may not be the same as that in the adult. Such judgments must be made in implementing systems for radiation protection. For radiation protection purposes, therefore, the relative biological effectiveness of these radiations at relevant doses and dose rates, without regard to specific biological endpoints, are specified through the use of w_R (ICRP, 1991a; NCRP, 1993).

6.4.3 Cell Migration and Differentiation

The embryo/fetus offers unique challenges for relating radiation dosimetry to the consequences of radiation, especially with radionuclides. During organogenesis and histogenesis the cells change position as they reorganize into the final organs and tissues and differentiate into new tissues. This may lead to movements of incorporated radionuclides during cell or tissue reorganization beyond those attributable to diffusion or other physical mechanisms. In addition, the consequences of a radiation dose to a cell population may be expressed in a location other than where the dose was absorbed and may affect more than one tissue or cell type.

These phenomena are mentioned because, while little research has been conducted in this area, they may bear significantly upon the work presented here and on the resultant radiation effects.

6.5 Effects of Internally Deposited Radionuclides

As noted above, estimation and expression of radiation absorbed dose to the embryo/fetus is significantly more complicated with internal radionuclides than with external penetrating radiations (Sikov, 1992a). Complications lead to several factors that make it impossible to develop generalized relationships that can be accurately applied to all radionuclides. These factors include differences in the degree to which materials cross the placenta, the resulting radionuclide levels in the conceptus, and the fact that many radioisotopic materials of concern have specific affinities and localize in characteristic organs or tissues of the conceptus and throughout the fetoplacental unit.

Further, transfer is influenced by the physical, chemical and physicochemical state of the radionuclides, and the effect of gestational stage at exposure on placental structure and function. Many of the relevant radionuclides emit beta or alpha particles. The size of the organ or tissue of deposition often is small so that a substantial fraction of the emitted radiation may not be absorbed within the volume of origin. Estimations of tissue concentrations or activities and resulting radiation doses are complicated by the interplay of affinities, translocations and growth. Moreover, the exposures may involve protraction in time with exposure of multiple gestational stages and selective exposure of specific structures, some of which may be transient in nature.

As a simplified and generalized overview of the relationships pertaining to radionuclide exposure, we may consider that there is a complex interplay between maternal biokinetics, placental transfer, and the presence of receptor sites or preferential tissues of deposition in the conceptus. Fetal concentrations may reach relatively high levels for substances such as tritiated water, which is uniformly distributed. Tritium, in organic forms, is often less readily transferred but it may be selectively incorporated into particular tissues and metabolic pathways. Iodide ions are readily transferred across the placenta and, depending on stage of gestation, are incorporated into the fetal thyroid. Elements such as iron, strontium, calcium and several others are reasonably accessible to the conceptus, but their kinetics and deposition are influenced by

development of hemoglobin synthesis and ossification sites, respectively, which progress with stage of gestation. Many heavy elements, including transuranics, are transferred to a low degree although there is a wide range in the actual values.

Empirical studies have shown that high amounts of some radionuclides, such as ^3H , ^{32}P and ^{90}Sr , are embryotoxic and teratogenic when administered during organogenesis. There seems to be reasonable dosimetric compatibility of effects with those produced by external photon exposure when allowance is made for differences in dose partition, rates and protraction. Several elements of higher atomic number have been shown to be embryotoxic and weakly teratogenic in rodents, but this occurs only at high administered levels of radionuclide. Data are not available for all elements in the actinide series, but for some nuclides such as plutonium, embryo-toxicity occurs *via* an effect on the villus yolk sac which has a high affinity for heavy metals and is an important absorptive structure in the early rodent embryo. The nutritive role of this structure may not be as persistent in higher mammals, including humans, as in rodents, but the high affinity has been demonstrated in nonhuman primates.

Specific localization may have even more marked influences on effects after the target tissues have developed. For example, radio-iodines can reach higher concentrations in the fetal thyroid than in the maternal thyroid of both laboratory animals and humans. Animal experiments have demonstrated both acute and subacute changes in thyroid morphology and physiology as a consequence of such exposures, and long-term effects such as increased thyroid tumor incidences have been detected in animal experiments. Likewise, incorporation of radiophosphorus or radiostrontium into developing bone can lead to skeletal malformations. Strontium-90 can lead to bone tumors as well as to pituitary tumors. The latter presumably are a result of high radiation doses from strontium localization in the sella turcica (the bony structure surrounding the pituitary gland) (Schmahl *et al.*, 1979).

The origin of progenitor cells of the gametes and hematopoietic lines in blood islands of the visceral splanchnopleure, or yolk sac, must be considered in evaluating the dosimetry and effects of internal exposures from some radionuclides. Elements that localize in the yolk sac could adversely affect its structure and function and selectively irradiate primitive stem cells. Data apparently have not been reported (but effects have not been specifically searched for) to suggest that such exposures lead to effects such as premature loss of reproductive function, accelerated decline of the

hematopoietic system, or increased incidences of neoplasms of blood-forming tissues.

Tumor development following prenatal and/or neonatal exposure of animals has been studied for a limited number of radionuclides: tritium, phosphorus, strontium, iodine and plutonium (Sikov, 1989). The several factors considered above obviate derivation of direct relationships between maternal exposure, prenatal radionuclide concentrations, and radiation doses to target tissues. Specific dose-effect relationships differ among radionuclides and change with differences in the developmental stages exposed. In general, however, most studies have found dose-related increases in the incidence of tumors or decreases in age at tumor appearance among animals that received prenatal and/or neonatal radiation exposures from internally deposited radionuclides. Decreased tumor incidences also have been reported, especially at high-dose levels; these were sometimes attributable to cell death or inhibited development of target tissues.

Endocrine malfunction, particularly of the ovaries, after acute x-ray or chronic tritiated water exposures, has been associated with decreased mammary tumor incidences. Radiation doses to perinatal animals and to their individual tissues relative to the administered activity are usually less than the corresponding radiation doses to their dams or to older animals. As a result, perinatal animals sometimes appear to be less sensitive to late effects than are adults when the responses are compared on the basis of administered radioactivity. Perinatal animals are usually found to be more susceptible to tumorigenesis by radiation, especially from internal radionuclides when the responses are expressed relative to radiation absorbed doses (Sikov, 1989; 1992a).

Age-related differences in predominant tumor types and/or sites of tumor development are often found associated with exposure to many radionuclides. These differences, as well as the existence of nuclide-specific target organs or tissues are explainable by dosimetric factors and developmental considerations. Inhomogeneities of tissue radiation doses, increased effectiveness of some particulate radiations, and protraction of the radiation exposure from internal radionuclides may lead to apparent differences in sensitivity relative to acute exposures from external photon beams, although the physical interactions with tissue are the same.

7. Factors to Establish Fetoplacental Concentrations and Radiation Doses

7.1 Modeling and Kinetics

7.1.1 Modeling

For many substances, especially radionuclides, the kinetics of distribution within the human body are fairly well known from direct measurement or by extrapolation from animal experiments. In particular, the concentration of radioactive material in blood can be expressed as a function of time. In principle, it is possible to regard the human body as a system of compartments or regions within which a substance may reside. In schematics, the compartments are represented, for example, by rectangles connected by arrows representing the transfer of the substance into and out of the system and between compartments (e.g., Figures 7.1 and 7.2). When the sizes of the compartments and the transfer rates are known, the concentration of the substance within the various compartments can be represented by a set of coupled differential equations (e.g., Equations 7.1 and 7.2). The solution of this set of equations describes the time course of a substance introduced into one or more of the compartments. Alternatively, if the time course of distribution in the compartments is known, then the inverse procedure can be used to determine the compartment sizes and the transfer rates.

Consideration of the kinetics in a pregnant woman involves additional complications associated with progressive changes in her organ sizes, blood flow, and physiology/biochemistry. Some fraction of the material in maternal tissues may be transferred across the placenta and into the fetus so that placental transfer and distribution of the substance within the fetus also affect the maternal

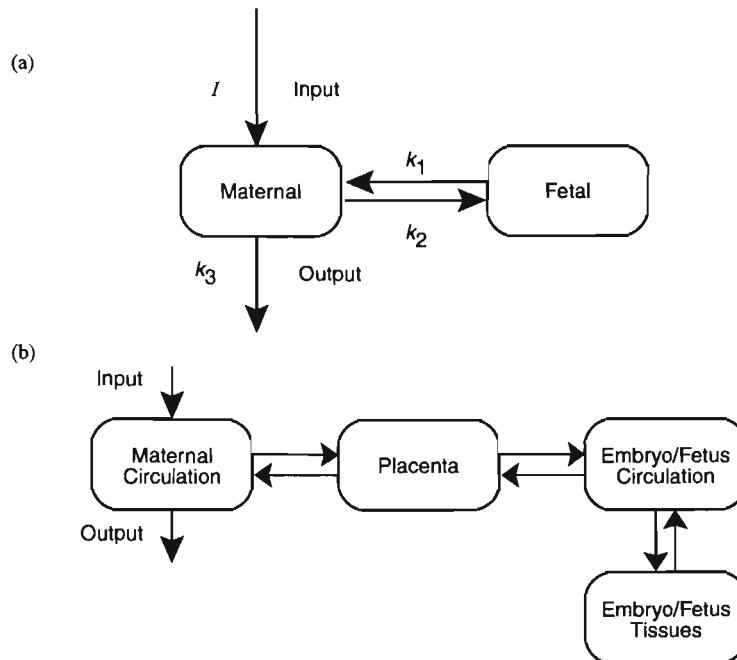


Fig. 7.1. (a) Two compartment open system model for maternal-fetal exchange. (b) Four-compartment model for maternal-fetal exchange.

kinetic model. Transfers in the reverse direction may occur, so the amount of material present at any time in the fetus is the difference between the amount that has entered and that which has left the fetus. The kinetics during pregnancy introduce an additional set of transfer rates and compartments that are not present in the nonpregnant woman. In general, limited data are directly available for describing the time course of the distributed radionuclides in the fetus. Frequently, the available data are insufficient to allow analysis of the fetal kinetics in terms of a multiple compartment model so that the use of a simplified compartmental model is most appropriate.

Several models for the transfer of material between the maternal and fetal circulations have been published. These models frequently contain several compartments (maternal intracellular, maternal extracellular, amniotic fluid, placenta, fetal extracellular, and fetal intracellular) and pathways of transfer. Sikov and

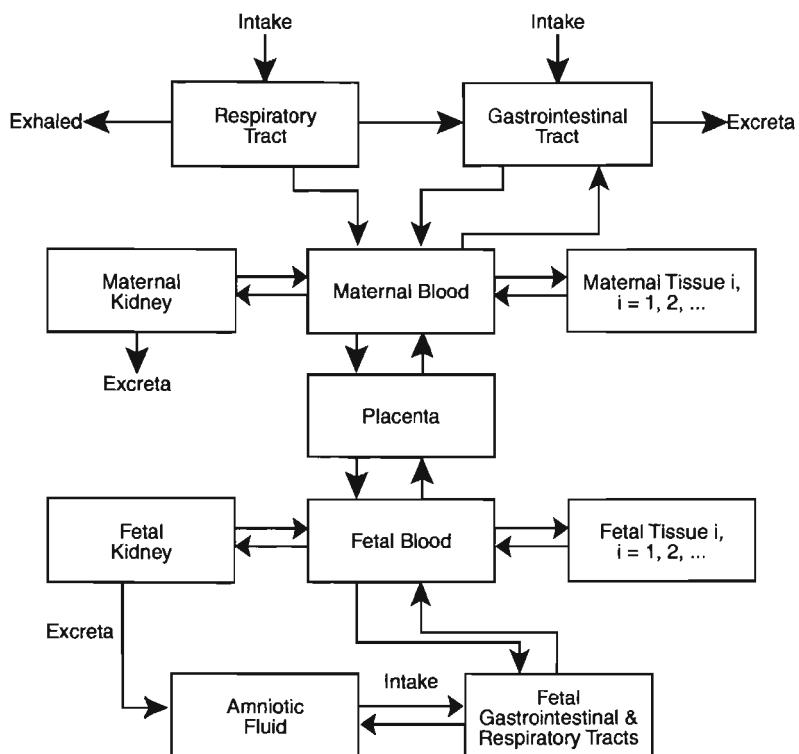


Fig. 7.2. Compartment model depicting the maternal-fetal exchange of radionuclides ingested or inhaled by the mother. The largest fractions of radionuclides removed from fetal tissues are considered to return to the maternal circulation. The fetus may eliminate radionuclides *via* urinary or fecal excretion with a potential for a subsequent intake in ingested or inhaled amniotic fluid.

Kelman (1989) suggested, for example, such a model. They also presented a three-compartment closed system (pregnant woman, placenta and embryo/fetus). For substances for which only the net transfer to the fetus is known, or when data are known for only a few times, even these models are too complex for kinetic analysis. Thus, for many substances a two-compartment open system, such as shown in Figure 7.1, is adequate for fitting the available data.

The kinetics of Figure 7.1 can be expressed as a set of coupled, linear first-order differential equations:

$$\begin{aligned}\frac{dM}{dt} &= I + k_1F - k_2M - k_3M \\ \frac{dF}{dt} &= k_2M - k_1F\end{aligned}\quad (7.1)$$

where:

- M = amount of the substance in the maternal system
- F = amount of the substance in the fetus
- I = input rate

The transfer rate constants (k_1 , k_2 and k_3) denote the fractional rate of transfer of the substance in a particular pathway and t represents time. The solution of this set of equations describes the amount of activity in the fetus and mother as a function of time. The solution for the fetus (F) has the form:

$$F(t) = a_1e^{-\lambda_1 t} + a_2e^{-\lambda_2 t} + E \quad (7.2)$$

where:

- E = equilibrium value determined by I and k_3
- a = coefficients
- λ = disappearance constants
- e = natural logarithm base
- t = time

The a 's and λ 's are complicated functions of the k 's in Equation 7.1. The intermediate steps in deriving Equation 7.2 from Equation 7.1 have been discussed by Robertson (1957; 1983). The components of Equation 7.2 may be determined empirically by fitting the equation to the experimental data. The time integral of $F(t)dt$ in Equation 7.2 is the cumulated activity (or number of nuclear transformations), which is a key factor in the equation for calculating the radiation dose as discussed in Section 7.2.

In an example of these techniques, Neslen *et al.* (1954) used a two-compartment closed model to analyze the data in studies of sodium and potassium exchange between amniotic fluid and the maternal system in two pregnant women near term. They found that the same percentage of sodium and potassium was exchanged per unit of time, while that for deuterium was five times greater. In absolute terms, the exchange rates were calculated at 31.9 moles of water, 0.014 mole of sodium, and 0.00041 mole of potassium per hour.

When more complete data are available, a somewhat more complicated model, such as the four-compartment closed system shown in Figure 7.1b can be used. That model can also be considered as

a four-compartment open system by including the I and k_3 components.

Analytical solutions of the equations describing such a system have been published but are quite unwieldy. In practice, for complex compartmental systems, such as shown in Figure 7.2, recourse must be made to numerical methods to solve the set of differential equations. Suitable numerical methods are available and a number of computer-assisted approaches have evolved for such purposes. These include the SAAM program that is widely used for nuclear medicine purposes, as described by Foster and Boston (1983). Examples include the work of Ramberg *et al.* (1973) who used the SAAM program to calculate transfer rates in a study of calcium transport across the sheep placenta. Their model includes three maternal, two placental, and three fetal compartments, which they state is the simplest compartmental construct that fits the data.

The Stella modeling language provides a computer program that develops and numerically solves sets of time-related equations when compartment sizes, fractional movements, and rates are entered (Hannon and Ruth, 1994; Peterson and Richmond, 1994). Sikov and Hui (1996) used the Stella program, together with direct data and extrapolations from the physiological and developmental biology literature to estimate gestational-stage-related fractional deposition values in the embryo/fetus as well as to integrate under the resulting curves to estimate radiation absorbed doses.

For calculating fetal thyroid and whole-body doses from ^{131}I , Zanzonico and Becker (1992) used a six-compartment model adapted from one previously proposed by Johnson (1982) by introducing a slow placental exchange between the maternal and fetal protein bound iodine and using fetal age-dependent rate constants for fetal thyroid function. VanKreel (1981) discusses two- and three-compartment models that take into account metabolism occurring during transport.

7.1.2 Kinetics

Relatively few studies of placental transfer in animals have yielded kinetic data that are directly applicable to humans. However, animal studies can be used for extrapolations on the basis of comparative anatomy, general principles of systemic physiology, and the physiology of placental transfer. Human studies that provide kinetic data are described in Appendix A. Examples include the report of Tawada *et al.* (1985) who studied placental transport mechanisms for iron. Likewise, Roels *et al.* (1978) reported on

factors affecting placental transfer of lead, mercury, cadmium and carbon monoxide. Pitkin *et al.* (1970) studied placental transmission and fetal distribution of cyclamate.

Page (1957) proposed a classification scheme based on a combination of the embryo/fetal utilization and the transport categories of materials across the human placenta: (1) primary physiologic significance of the substances transferred, (2) corresponding relative rates of their transfer, (3) actual mechanisms of transport, and (4) equality or inequality of distribution. Their categorization is summarized as follows:

Group I. Substances concerned with the maintenance of biochemical homeostasis. The rates of transfer of such substances are typically on the order of milligrams per second with rapid diffusion being the predominant mechanisms of transport:

1. equilibrium is readily attained; e.g., water and electrolytes
2. unequal distribution due to differences in rates of removal and/or different dissociation constants of complexes formed; e.g., oxygen and carbon dioxide
3. unequal distribution due to destruction by the placenta; e.g., amines

Group II. Substances concerned primarily with fetal nutrition. The rates of transfer of such substances are typically on the order of milligrams per minute with carrier systems (plus diffusion) being the predominant transport mechanism:

1. carrier systems operating equally in both directions; e.g., glucose
2. carrier systems operating against a concentration gradient; e.g., amino acids
3. unequal distribution with resultant molecular alteration during active transport; e.g., riboflavin

Group III. Substances concerned primarily with modification of fetal growth and the maintenance of pregnancy. The rates of transfer of such substances are typically on the order of milligrams per hour with slow diffusion being the predominant mechanisms. Examples include steroid and protein hormones of maternal or placental origin.

Group IV. Substances of immunologic importance only. The rates of transfer of such substances are typically on the order of milligrams per day with leakage through large pores, droplet transfer, and possibly pinocytosis, being the mechanisms of transport:

1. cell transfer, *e.g.*, by red blood cells
2. pinocytosis, *e.g.*, by plasma proteins

7.1.3 Maternal and Fetoplacental Dynamics

The classification described by Page (1957), which is derived from the general systematics as well as details of fetoplacental physiology, has provided guidance for subsequent analyses. Physiologically based pharmacokinetic (PBPK) models have proven to be useful tools in computing the distribution and concentration of chemicals among organs of the body as a function of time (Bischoff *et al.*, 1986). In PBPK modeling, the disposition of a substance is described by a dynamic mass balance between its concentration in the blood entering and leaving an organ or tissue. Increasingly complex models are being developed for pregnancy. Luecke *et al.* (1995) described a detailed model that included consideration of changes that take place in the woman, the placenta, and the embryo/fetus over the period. The resultant model includes 27 compartments in the woman and 16 in the fetus.

Changing sizes and shapes of the woman, embryo/fetus, and fetal organs should be included in the kinetic modeling as well as the dosimetry. Progressive metabolic changes in fetal tissues such as thyroid, liver and bone can lead to markedly nonuniform distribution in the fetus and also have profound effects on the kinetics (Munro and Eckerman, 1998). Integration of these factors would help quantify placental transfer as well as the disposition of radionuclides in the woman and in the embryo/fetus. As mentioned in the previous section, computer programs are becoming increasingly available for analysis of such complex compartmental models.

7.2 Dosimetry

Both MIRD and the ICRP have advanced methods for calculating the radiation dose to humans from radionuclides distributed within the body (ICRP, 1979; 1991b; Loevinger and Berman, 1988; Loevinger *et al.*, 1991). The estimates of radiation dose are derived using mathematical models of the human anatomy which represent the body and its organs by relatively simple geometric figures, such as ellipsoids, spheres, cylinders and cones (ICRP, 1979; C[h]risty and Eckerman, 1987; Snyder *et al.*, 1969). A comprehensive mathematical model of the pregnant woman at representative gestational stages is also available (Stabin *et al.*, 1995) and a series

of anatomical models of the fetus at various times post conception is under development.¹ These anatomical models are used with Monte Carlo methods to evaluate the transport and deposition of energy within the body for electron, photon and neutron radiations.

MIRD defined a schema for estimating the mean absorbed dose from radionuclides in target regions of interest from radionuclides residing in various source regions (Loevinger and Berman, 1988). The source and target regions can be the same regions or regions separate from each other. In 1979, the ICRP, in Publication 30, published a methodology which extended the MIRD schema to calculate the dosimetric quantities of interest in radiation protection of workers (ICRP, 1979). The ICRP further extended the methodology in Publications 56 and 67 to address the dose to individuals of various ages, including infants and children (ICRP, 1989; 1993).

The ICRP and MIRD dosimetric methodologies differentiate two sets of anatomical regions in the body. One set, the source regions or organs, specifies the locations where the radionuclide resides during its residence in the body. The regions included in this set reflect the route of entrance or intake of the radionuclide into the body, the kinetics of distribution of the radionuclide within the systemic region, and the routes of elimination or excretion of the radionuclide. No constraints are placed on the nature of the source regions; however, the dosimetric consideration requires a correspondence with identifiable anatomical regions. Within the specified anatomical regions, the radionuclide may be distributed uniformly on surfaces (e.g., in the airways of the lung), distributed uniformly within the volume, or distributed uniformly within the contents of the organ (e.g., urinary bladder contents). The second set is the target regions or organs for which radiation doses are of interest. The ICRP methodology focuses on those tissues of the body that are at radiological risk and its expressions of dose are based on the relative biological effectiveness of the various radiations and the health detriment associated with the irradiation of the different tissues of the body. The MIRD methodology considers only absorbed dose (energy deposited per unit mass) and does not include any information regarding effect.

¹Eckerman, K.F. (1997). Personal communication (Oak Ridge National Laboratory, Oak Ridge, Tennessee).

7.2.1 Dosimetric Quantities

The physical dosimetric quantity in both the MIRD and ICRP methodologies is the absorbed dose. The absorbed dose, D , is defined as the energy absorbed from ionizing radiation per unit mass. More precisely the absorbed dose is defined as $D = d\bar{\epsilon}/dm$, where $\bar{\epsilon}$ is the mean energy imparted by ionizing radiation to an element of matter of mass dm . In practice the mean absorbed dose, \bar{D} , is averaged over the mass of the organs or tissues of interest. That is, \bar{D} is the energy absorbed within the target region divided by the mass of the target.

In radiation protection, equivalent dose is the basic dosimetric quantity. The equivalent dose, H_T , in tissue T is the mean absorbed dose, \bar{D} , within the tissue weighted for the quality of the absorbed radiation. The weighting factor used for this purpose, w_R , is selected for the type and energy of the radiation incident on the body or, in the case of sources within the body, emitted by the source. The equivalent dose, H_T , is defined as:

$$H_T = \sum_R w_R \bar{D}_{T,R} \quad (7.3)$$

where:

$\bar{D}_{T,R}$ = the mean absorbed dose from radiation R in target tissue T (see Table 7.1)

w_R = the radiation weighting factor, a factor that accounts for differences in biological effectiveness between different radiations

The third dosimetric quantity of radiation protection is the effective dose, E . This quantity is the weighted sum of the equivalent dose in the tissues of the body given as:

$$E = \sum_T w_T H_T \quad (7.4)$$

where:

w_T = the tissue weighting factor, which represents the relative contribution of tissue T to the total health detriment when the body is uniformly irradiated

The numerical values of w_T , shown in Table 7.2, are derived from the radioepidemiological studies of populations generally irradiated as adults. The ICRP considered that adjustments of w_T were not warranted in applications to populations including children (ICRP, 1993).

Table 7.1—*Radiation weighting factors (w_R) (NCRP, 1993a).*

Radiation Type and Energy	w_R
Photons, all energy	1
Electrons and muons	1
Neutrons, energy: <10 keV	5
10-100 keV	10
100-2,000 keV	20
2-20 MeV	10
>20 MeV	5
Protons, energy: >2 MeV	5
Alpha particles, fission fragments, heavy nuclei	20

The equivalent and effective dose quantities are quantities of radiation protection which provide, only in a very general manner, an assessment of health risk. Quantification of the health consequence of *in utero* exposures may be better represented through consideration of the distribution of the absorbed dose, the relative biological effectiveness of the radiations of concern, and the relevant probability coefficients for a health detriment.

7.2.2 Dosimetric Formulations

The basic formulations of the absorbed dose and equivalent dose in the MIRD and ICRP methodologies are:

$$\bar{D}(k) = \sum_h \tilde{A}_h S(k \leftarrow h) \quad \text{MIRD} \quad (7.5a)$$

$$H_T = \sum_S U_S SEE(T \leftarrow S) \quad \text{ICRP} \quad (7.5b)$$

where for the MIRD equation:

$\bar{D}(k)$ = mean absorbed dose in target region k

\tilde{A}_h = time integral of activity in source region h

S = absorbed dose rate in target region k per unit intake of activity in source region h

In the ICRP equation:

H_T = equivalent dose in target organ T

U_S = number of nuclear transformations of the radionuclide occurring in source region S

SEE = specific equivalent energy absorbed in target region T per nuclear transformation in source region S

Table 7.2—*Tissue weighting factors (w_T).*

Tissue or Organ	w_T
Gonads	0.20
Active bone marrow	0.12
Colon	0.12
Lung	0.12
Stomach	0.12
Bladder	0.05
Breast	0.05
Liver	0.05
Esophagus	0.05
Thyroid	0.05
Skin	0.01
Bone surface	0.01
Remainder	0.05

The distribution kinetics and the radiological half-life of the radionuclide determine the activity time integral or number of nuclear transformations in the source region. A_h and U_S both represent time integrals of the activity residing in the source region S.

The equation describing S of the MIRD formulation is:

$$S(k \leftarrow h) = \sum_i \Delta_i \Phi_i (k \leftarrow h), \quad (7.6)$$

where:

- Δ_i = the mean energy of the radiation type i emitted per nuclear transition
- Φ_i = the specific absorbed fraction in energy applicable to radiation

The corresponding formulation of the age-dependent SEE quantity in the ICRP methodology is:

$$SEE(T \leftarrow S; t) = \frac{1}{M_T(t)} \sum_R E_R Y_R w_R A F_R(T \leftarrow S; E_R, t), \quad (7.7)$$

where:

- E_R = the energy of radiation R emitted by the radionuclide
- Y_R = yield of radiation R per nuclear transformation of the radionuclide
- $M_T(t)$ = the mass of the target tissue T at age t
- w_R = the radiation weighting factor applicable to radiation R

$AF_R(T \leftarrow S; E_R, t)$ = the absorbed fraction quantity representing the fraction of the energy E_R emitted in S that is absorbed in T for an individual of age t

7.2.3 Energy Emitted per Nuclear Transition

Several tabulations of the energies and intensities of the radiations emitted by radionuclides undergoing nuclear transitions (also referred to as nuclear transformation or simply decay) are available (ICRP, 1983; NCRP, 1985; Weber *et al.*, 1989). ICRP Publication 38 (ICRP, 1983) tabulates data for over 800 radionuclides while the monograph *MIRD: Radionuclide Data and Decay Schemes* (Weber *et al.*, 1989) provides decay data on 242 radionuclides. These data, including the beta spectra, are also available in electronic form (Eckerman *et al.*, 1994).

7.2.4 Masses of the Target Regions

The masses of the woman and the embryo/fetus at different stages of pregnancy can be derived from data in ICRP Publication 23 (ICRP, 1975), Chisty and Eckerman (1987), Stabin *et al.* (1995), and anatomy textbooks (e.g., Hytten and Chamberlain, 1991). Representative values are given in Table 7.3a and 7.3b, including masses of the human embryo/fetus and the pregnant woman at several stages of pregnancy (Sikov *et al.*, 1992a).

An extensive compilation of biometric data for the fetus has recently been published by Guihard-Costa *et al.* (1995). Their analysis involved nearly 5,000 fetuses, some studied postmortem and others by ultrasound. The biometric measures of particular utility in developing a three-dimensional model of the fetal anatomy for dosimetric computations included the postmortem measures of body and brain masses; postmortem measures of crown-to-rump length, crown-to-heel length, foot length, and head circumference; and ultrasound measures of the femur length, abdominal transverse diameter, biparietal diameter, and fronto-occipital diameter.

Fetal organ masses derived from autopsies are typically reported in the literature relative to body mass. Guihard-Costa *et al.* (1995) measured the mass of the brain in 291 samples weighted prior to

Table 7.3a—*Assumed physical characteristics of fetus.*

Gestation (d)	Length (cm)	Mass (g)	Semimajor Axis (cm)	Seminor Axis (cm)
30	0.4	0.353	0.2	0.2
60	3.3	10.7	1.7	0.9
90	10.6	71	5.3	1.1
120	18.9	276	9.5	1.9
150	26.8	617	13	2.7
180	33.7	1,140	17	3.4
210	39.8	1,951	20	4.1
240	45.1	2,876	23	4.6
270	49.6	3,471	25	5.1

Table 7.3b—*Assumed physical characteristics of mother and uterus.*

Gestation (d)	Mass (g)			
	Uterus and Contents	Total Soft Tissue	Maternal Skeleton	Pregnant Woman
0	80	53,000	5,000	58,000
30	330	53,250	5,000	58,250
60	580	53,500	5,000	58,500
90	830	53,750	5,000	58,750
120	1,190	54,110	5,000	59,110
150	1,690	54,610	5,000	59,610
180	2,420	55,340	5,000	60,340
210	3,450	56,370	5,000	61,370
240	4,920	57,840	5,000	62,840
270	7,030	59,950	5,000	64,950

fixation and 432 samples which were fixed for 4 to 10 weeks. The masses of the brain given in Table 7.4 were based on these data. Fetal thyroid masses have been reported by Costa *et al.* (1986), Aboul-Khair *et al.* (1966), Evans *et al.* (1967), and Ares *et al.* (1995). The data of Table 7.4 are based on an analysis of these data. For fetal organs, other than the brain and thyroid, the mass values in Table 7.4 were obtained from autopsies (Burdi *et al.*, 1981; Hudson, 1965; Jackson, 1909; Potter and Craig, 1975; Shepard *et al.*, 1988; Trotter and Peterson, 1968; Widdowson and Dickerson, 1964). Luecke *et al.* (1995) analyzed these data using an allometric relationship. The masses of the adrenals, bone, red marrow, heart, kidneys, liver, lungs, pancreas, spleen and thymus in Table 7.4 were

Table 7.4—*Fetal organ mass at various fetal ages.*

Organ	Mass (g)					
	10 weeks	15 weeks	20 weeks	25 weeks	30 weeks	38 weeks
Adrenal	0.06	0.38	0.99	1.9	3	5.8
Brain	6.4	22	59	118	192	352
Breast	0.0007	0.0054	0.016	0.031	0.052	0.11
ST wall	0.043	0.33	0.93	1.9	3.1	6.4
SI wall	0.22	1.7	4.7	9.5	16	33
ULI wall	0.071	0.53	1.5	3.1	5.1	11
LLI wall	0.054	0.4	1.2	2.3	3.9	8
Heart wall	0.19	1.4	3.8	7.6	13	25
Kidneys	0.12	1.2	3.5	7	12	23
Liver	0.81	6.1	17	35	59	120
Lungs	0.53	4.9	13	22	32	51
Ovaries	0.0022	0.017	0.047	0.095	0.16	0.33
Pancreas	0.39	0.86	1.3	1.7	2.1	2.8
Red marrow	0.28	2.2	6.5	13	23	47
Bone surface	0.1	0.76	2.2	4.4	7.3	15
Skin	0.8	6	17	34	57	119
Spleen	0.0035	0.069	0.36	1.1	2.7	9.1
Testes	0.0057	0.043	0.12	0.25	0.41	0.84
Thymus	0.041	0.39	1.3	2.8	5.1	11
Thyroid	0.022	0.077	0.18	0.36	0.63	1.3
Urinary bladder	0.020	0.15	0.42	0.84	1.4	2.9
Total body	21	164	483	992	1,693	3,544

adjusted to be consistent with the values in the newborn (Christy and Eckerman, 1987; ICRP, 1989). The masses of breast tissue, the segments of the GI tract, ovaries, testes, skin and urinary bladder were derived by scaling their mass in the newborn as a power function of body mass; that is, as:

$$m_T(t) = \left[\frac{m_t}{m_{TB}^{0.9714}} \right]_{\text{newborn}} m_{TB}(t)^{0.9714} \quad (7.8)$$

where:

$m_{TB}(t)$ = the mass of the fetus at the age t of interest and the value of the exponent (0.9714) is the average value in the analysis of Luecke *et al.* (1995)

7.2.5 Absorbed Fraction and Specific Absorbed Fraction

The radiations emitted by radionuclides are often characterized in terms of their penetrating nature. Radiations which deposit their energy within the region in which they originated (within the source region) are termed nonpenetrating radiations. If the dimensions of the source region are large, relative to the range of the radiation, then essentially all of the emitted energy is absorbed within the source region and no energy will be absorbed in any other target regions. That is, the absorbed fraction ϕ (or AF) will be one if the source and target regions coincide and zero for target regions which share no points in common with the source region. Alpha and beta rays and photons (electromagnetic radiation) of energy less than 10 keV are usually classified as nonpenetrating.

If a substantial fraction of the emitted energy escapes the source region within which it originates, then the radiation may deposit energy in target regions remote from the source region. Photons of energy greater than 10 keV and neutrons are considered to be penetrating radiations.

Several MIRD pamphlets (Brownell *et al.*, 1968; Snyder *et al.*, 1969; 1975; 1978) provide data on the absorbed fraction, specific absorbed fractions, and S values for photons that can be incorporated into the equations for calculating estimates of absorbed dose. However, none of these pamphlets gives information that directly pertains to the pregnant woman or the embryo/fetus. The S values for the uterus in MIRD Pamphlet No. 11 (Snyder *et al.*, 1975) have often been used for calculating the dose to the embryo/fetus during the first three months of pregnancy from activity residing in other organs. However, that publication does not provide S values for the uterus as a source organ. Some publications contain estimates of the energy absorbed by the embryo/fetus based on modifications of the Reference Man model (Cloutier *et al.*, 1973a; 1976; Smith and Warner, 1976). Information needed to calculate the absorbed fractions for beta and electron radiations as penetrating radiations can be found in the literature (Berger, 1970; Loevinger *et al.*, 1956; 1991; Sikov *et al.*, 1992a).

C[h]risty and Eckerman (1987) published specific absorbed fractions for photon emissions in a Reference Woman model which includes the uterus both as a source and a target organ. Specific absorbed fractions for photon emission within models of the pregnant woman at the end of the first, second and third trimesters have been published (Davis *et al.*, 1987; Stabin *et al.*, 1995; Watson and Stabin, 1987; Watson *et al.*, 1990). These data are useful for calculating the radiation dose to the uterus plus embryo/fetus from

radionuclides in the mother's body and the radiation dose to the fetus from radionuclides uniformly distributed throughout the uterus including the embryo/fetus. MIRD Pamphlets No. 3 and No. 8 contain absorbed fraction data for photons in spheres and ellipsoids that can be used for calculating the dose to the fetus from the photons emitted by radionuclides residing in the fetus (Brownell *et al.*, 1968; Ellett and Humes, 1971).

The dose to the fetus for each month of pregnancy from radionuclides in the mother's urinary bladder can be calculated from factors published by Cloutier *et al.* (1973a). Doses to specific organs of the fetus were not calculated. However, the fetal space was divided into 12 regions and the average doses per photon emitted from the urinary bladder contents are listed for each region, for the entire fetal space, and for the uterus. A procedure was also given for calculating the number of photons emitted from bladder contents when total body retention can be represented by a sum of exponentials. Elsasser *et al.* (1986) provided S values for self-irradiation of the embryo/fetus by ^{59}Fe , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{123}I , ^{131}I and ^{201}Tl . Other reports that give estimates of absorbed dose to the embryo/fetus from radionuclides have been published (Cloutier *et al.*, 1976; Sikov and Hui, 1996; Smith and Warner, 1976). The specific absorbed fraction data of Stabin *et al.* (1995) have been included within the MIRDOSE 3 computer program (Stabin, 1996) to facilitate calculation of radiation absorbed dose.

7.2.6 Cumulated Activity and Number of Nuclear Transformations

As shown in Equation 7.5 the calculation of radiation dose requires information on the cumulated activity or total number of nuclear transformations in the source regions with respect to time. The cumulated activity in a source region, \tilde{A}_h , can be derived by integrating the activity, $A_h(t)$, as a function of time t , in the source region over the time interval of interest. Thus the cumulated activity is:

$$\tilde{A}_h = \int_{T_1}^{T_2} A_h(t) dt \quad (7.9)$$

where the integral is over the time interval of interest. The MIRD committee (Loevinger *et al.*, 1991) typically takes as the beginning of the interval of interest (the lower limit of the integral) the zero time and the end of the interval (the upper limit of the integral) as

infinity. The upper limit is only appropriate if the radionuclide is short-lived or its residence time within the body is brief. In addition, the cumulated activity is only applicable in Equation 7.5a if changes in the anatomical parameters during the time of integration can be neglected. These conditions are typically satisfied in nuclear medicine. However, many of the radionuclides of interest in radiation protection are long-lived so that a finite upper limit of integration must be established. For example, the ICRP computes the number of nuclear transformations in source regions as the integral of the activity over a time period of 50 y following the intake of the radionuclide or till age 70 y, in the case of intakes by members of the public. Note that the cumulated activity \tilde{A}_h and U_S both represent an integral of the activity within the source regions. Similarly, the cumulated activity in the source organ, \tilde{A}_h , divided by the administered activity, A_0 , is equal to the residence time, τ_h , or average time the radionuclide remains in the source organ. Thus:

$$\tau_h = \frac{\tilde{A}_h}{A_0} \quad (7.10)$$

Cumulated activity, residence time, and number of nuclear transformations can be estimated by several techniques (Loevinger *et al.*, 1991), including compartmental modeling as described in Section 7.1, Modeling and Kinetics. The metabolic (or biokinetic) models published by the ICRP in the Publication 30 series (ICRP, 1979; 1980; 1981) and in ICRP Publications 56 and 67 (ICRP, 1989; 1993) have been used to calculate the dose the fetus receives from activity residing in the mother.

7.3 Dosimetric Formulations for Embryo/Fetus

7.3.1 Current Dosimetric Formulations

The dosimetric formulations discussed above are readily extended to address the radiation dose to the embryo/fetus resulting from radionuclide intakes by the mother occurring prior to or during pregnancy. The formulations must permit an estimation of the dose to various tissue *in utero*, the period that is considered in this Report. They are useful for calculations during pregnancy and the postnatal period as well. The intrauterine period can be considered as two phases, embryonic and fetal.

During the embryonic period the embryo is closely surrounded by the maternal uterine tissues. Radionuclides may reach and be incorporated into the developing embryo by diffusion. The fetal period is characterized by rapid growth of the body and functional development of its tissues. During the fetal period, materials are transferred from maternal to fetal circulation and subsequently distributed among and retained within the growing fetal tissues. Radionuclides incorporated into fetal issues may be present at birth and hence contribute to dose in the postnatal period. In addition, radiation emitted by radionuclides residing in the maternal tissues, and contained in the maternal bladder, may contribute to the radiation dose to the developing embryo/fetus.

The dose rate experienced by the embryo is largely a consequence of radionuclides residing in maternal organs (sources external to the embryo) either as a result of intakes prior to pregnancy or during the pregnancy. The dose rate to the embryo during the embryonic period is typically estimated by that to the maternal uterus. Because of the small size of the embryo, self-shielding of the differentiating tissues can be neglected and hence all tissues of the embryo can be assumed to receive the same dose. The absorbed fraction data needed for this evaluation have been derived using the anatomical model for the woman of C[h]risty and Eckerman (1987) and were tabulated by Stabin *et al.* (1995). During this period (first eight weeks) the changes in the maternal anatomy are rather minor and thus the absorbed fractions can be assumed not to change with time. Concerns regarding use of the macroscopic absorbed dose quantity, noted above, are particularly relevant during this period.

During the fetal period, the dose rate in the fetal tissues results from radionuclides residing in the maternal tissues, the placenta, and the fetal tissues. Absorbed fraction data for the irradiation of the fetus by photon emissions originating in maternal tissues have been tabulated by Stabin *et al.* (1995) using a mathematical model of the pregnant female at the end of the first, second and third trimesters. Since the orientation of the fetus is not fixed relative to the maternal tissues, Stabin *et al.* (1995) averaged the absorbed energy over the fetus and assumed that all fetal tissues receive a similar dose.

However, the patterns of radionuclide deposition within the fetus will lead to nonuniform distributions of radiation dose among the fetal tissues. Anatomical models of the fetus at various gestational ages have been developed and calculations of the absorbed

fractions for photons and electrons are being performed.² The very small sizes of the fetal organs and tissues necessitate that absorbed fractions be calculated for electrons; *i.e.*, in these small organs, higher energy electrons are penetrating radiations.

The dose during the postnatal period results from activity that remains in the fetus at the time of birth. C[h]risty and Eckerman (1987) have tabulated the necessary absorbed fraction data for this time period.

The equivalent dose rates during the periods of interest can be calculated by application of Equation 7.3. That is, the equivalent dose rate, \dot{H} , in tissue, T, at any time, t (postconception or birth) is:

$$\dot{H}_T(t) = \begin{cases} \text{maternal} \\ \sum_S q_{S,M}(t) SEE(\text{uterus} \leftarrow S), 0 \leq t \leq 8 \text{ weeks (embryo)} \\ \text{maternal} \\ \sum_S q_{S,M}(t) SEE(\text{fetus} \leftarrow S; t) + \\ \text{fetal} \\ \sum_S q_{S,F}(t) SEE(T \leftarrow S; t), 8 < t \leq 38 \text{ weeks (fetal)} \\ \text{child} \\ \sum_S q_{S,C}(t) SEE(T \leftarrow S; t), t \geq 38 \text{ weeks (postnatal)} \end{cases} \quad (7.11)$$

where:

$q_{S,F}$ = the activity present in source region S of the fetus

$q_{S,M}$ = the activity present in source region S of the mother
(including the placenta)

$q_{S,C}$ = the activity present in source region S of the offspring

Note the SEE values for irradiation of fetal targets by maternal and fetal source regions are a function of the age of the fetus reflecting the changes in the mother's body and the growth of the fetus during the fetal period.

The piecewise nature of Equation 7.11 can result in discontinuities in the dose rate at the boundaries of the periods. For example, the dose rate may change markedly at birth since the maternal burden no longer contributes to the dose rate during the postnatal

²Eckerman, K.F. (1997). Personal communication (Oak Ridge National Laboratory, Oak Ridge, Tennessee).

period. Discontinuities in the dose rate between the embryonic and fetal periods are probably artifacts of the formulations. In any case, the dose rates during the various periods can be integrated in a piecewise manner to compute the equivalent dose in the tissues.

Radiation protection must also address radionuclides whose residence in the body is quite long and, hence, the concept of the committed dose is fundamental to radiation protection. The committed dose is the total dose expected to be received as a consequence of a particular action. Dose coefficients tabulated by the ICRP typically represent the committed equivalent dose and committed effective dose resulting from a unit intake. The committed equivalent dose to the offspring associated with the maternal intake of the radionuclide may be defined as the sum of the equivalent dose during the *in utero* period and the equivalent dose during the first 70 y of postnatal life. That is:

$$H_T(70) = \int_0^T \dot{H}_T(t) dt + \int_T^{38 \text{ weeks}} \dot{H}_T(t) dt + \int_{\text{birth}}^{70 \text{ y}} \dot{H}_T(t) dt \quad (7.12)$$

where T is the duration of the embryonic period and is typically taken as eight weeks, the upper limit of integration of the second integral is the duration of pregnancy (38 weeks) and the last integral represents birth to age 70 y. The committed equivalent dose coefficient, h_T , is obtained by dividing the committed equivalent dose by the administered activity or intake, I , of the mother:

$$h_t = \frac{H_T}{I} \quad (7.13)$$

The effective dose, E , would be given as:

$$E = \sum_T w_T h_T \quad (7.14)$$

7.3.2 Earlier Dosimetric Formulations

Roedler (1987) and Stather *et al.* (1992) proposed that the radiation doses to the fetus could be estimated from knowledge of the relative concentrations of the radionuclide in the maternal and fetal tissues. The approach assumes that the tissues of interest are not specifically associated with intake or excretion (lung, GI tract, or urinary bladder). Further, the approach is most meaningful for radionuclides that emit only nonpenetrating radiations and have half-lives that are sufficiently short that fetal growth can be

neglected. The ratio of the fetal to maternal radiation doses in the tissue of interest can be expressed as:

$$\frac{H_f}{H_m} = \frac{C_f}{C_m} \frac{T_f}{T_m} \frac{AF_f}{AF_m} \quad (7.15)$$

where:

f and *m* = fetal and maternal

H = the equivalent dose in the tissue of interest

C = the maximum concentration in the tissue

T = the effective halftime of the activity in the tissue

AF = the absorbed fraction in the tissue

The assumptions underlying this equation limit its applications to situations in nuclear medicine where the administered radionuclides are typically short-lived.

Examination of the literature reveals that biological halftimes in the human fetus have been established for relatively few elements. These include iodine and iron determined from medical uses of ^{131}I and ^{59}Fe , as well as strontium and cesium determined from fallout of ^{90}Sr and ^{137}Cs as a result of nuclear weapons testing (Roedler, 1987). Iodine-131 was also studied as a result of fallout from nuclear weapons. Because of the limited data regarding the biological halftimes in the fetus, application of this formulation usually equates the effective halftime with the physical half-life of the radionuclide; *i.e.*, it neglects biological removal processes.

Absorbed fractions for self-irradiation within the maternal tissues are available (Christy and Eckerman, 1987; Stabin *et al.*, 1995). Absorbed fractions for self-irradiation of fetal organs can be approximated using the data of Brownell *et al.* (1968) and Ellett and Humes (1971), together with information on masses of the fetal tissues (Table 7.4).

As was noted above, the dose to the uterus can be used as a surrogate for the dose to the embryo/fetus. This is primarily applicable during the first three months of pregnancy. In some instances, however, the uterine dose has been used to estimate the dose during the total gestational period.

Values of the committed equivalent dose or of the radiation absorbed dose to the uterus have been tabulated for various radionuclides and radiopharmaceuticals (ICRP, 1987; Eckerman *et al.*, 1988; STR, 1990; Watson *et al.*, 1992). Sikov and Hui (1996) calculated from Eckerman *et al.* (1988), the committed equivalent dose relative to the quantity of radioactivity entering systemic circulation (blood or the transfer compartment). These data are tabulated in Regulatory Guide 8.36 (NRC, 1992).

The use of surrogate values is appropriate when the placental transfer of the radionuclide is limited and the radiation exposure is largely due to photon emissions. Later in the pregnancy, the size and location of the uterus and its contents are poorly represented by the nongravid uterus. Use of absorbed fraction data for the uterus in models of the pregnant woman (Stabin *et al.*, 1995) would provide an improved surrogate.

7.4 Other Considerations

7.4.1 *Extrapolation of Animal Data*

Several methods have been proposed for extrapolating to humans, values for tissue concentrations and residence times of radionuclides determined in animal experiments (McAfee and Subramanian, 1981; Roedler, 1981; Thomas and Eberhardt, 1981). Each of these methods has weaknesses when used for extrapolating data from pregnant animals to the pregnant woman as noted in Section 5.3.3, Animal Subjects. Information about the amount of radionuclide in important source tissues must be obtained at a sufficient number of times to demonstrate changes in distribution and retention and permit the determination of cumulated activities or residence times in source organs for calculating radiation doses. Source tissues may include maternal organs, the placenta, tissues surrounding the embryo/fetus within the uterus, and the embryo/fetus itself.

Residence times found in the animal may be applied to the human by utilizing appropriate modifications to take into account differences in anatomy and physiology. Some modification methods are: (1) extrapolation of the long-term halftime of the retention function from animal to human by using a power function of the body mass (Stara *et al.*, 1971); (2) extrapolation of the residence time from animal to human by using a power function of the body mass (Roedler, 1981); and (3) extrapolation of the biological residence time from animal to human by using "similarity ratios" which require that data be collected in several animal species (Thomas and Eberhardt, 1976).

Serious errors may occur in extrapolating from animals to humans through the use of concentration data without appropriate normalization (Blau, 1975; Oldendorf, 1974). Oldendorf recommended that the individual tissue concentrations be expressed as a percent of mean body concentration. Other researchers have used

multiples of this expression such as percent kilogram dose per gram and the percent dose per one percent body mass. The percent dose per one percent body mass is 10 times the percent kilogram dose per gram and 0.01 of the mean body concentration. Allowances must be made for differences in the relative organ sizes of experimental animals and humans. For example, percent administered activity in the blood per one percent body mass of a mouse can be extrapolated to the percent of administered activity in the blood of a human by multiplying the mouse data by the percent that the human blood mass is of the total human body mass. This value varies by age and sex. If the fraction of absorbed radiation energy is determined for an anatomic model representing a reference human (Davis *et al.*, 1987; ICRP, 1975; Watson *et al.*, 1990), the data should be normalized to the masses in the model.

Conversion in the time dimension is often required in extrapolating from animals to humans. Many materials follow a pattern of rapid clearance from the blood and total body in small animals (rodents), intermediate clearances in larger animals (dog and monkey), and slow clearance in large primates and humans. Compensation for this is sometimes performed by the use of power functions of body mass or body surface area (McAfee and Subramanian, 1981).

The foregoing approaches to extrapolation or translation of numerical values of size, time or relative concentration from animal studies to human pregnancy mainly are based on conversion factors that were derived by manipulation of selected empirical relations. The use of PBPK models, discussed in Section 7.1, may provide additional relationships for extrapolation and provide functional bridges among the pharmacokinetics pertaining to different species. As such, they provide useful supplements to these other approaches.

7.4.2 *Fetal and Maternal Excretion*

In the mother, the primary route of excretion for many radioactive compounds is *via* the kidneys and urinary bladder. Excretion reduces the amount of radioactive material in the body, but photon emissions from radionuclides in the kidneys, bladder or GI tract can contribute to the radiation dose to the embryo/fetus. Excretion *via* other routes (perspiration and respiration) also reduces the effective half-times of retention of activity but otherwise does not have a significant effect on the radiation dose to the embryo/fetus.

In the embryo, by the eleventh week the heart has developed into a four-chambered organ and the circulatory pattern is established. Excretion by the fetus is primarily by transfer from the fetal circulation to the maternal circulation. The fetus also excretes urine and feces, which enter the amniotic fluid and may be swallowed or inhaled and reabsorbed into the fetal circulation (Figure 7.2).

7.4.3 *Role of Growth*

For radionuclides that have effective half-times longer than a few days, the growth of the embryo/fetus will affect their concentration in tissues. In addition, the absorbed fractions of energy will change as the embryo/fetus grow. These changes require calculation of absorbed fractions and absorbed dose rates at several time segments. Integration of these dose rates would provide a total dose over the entire time period of interest.

The specific absorbed fractions for photons (absorbed fractions per unit mass) are relatively insensitive to size, shape and position of source and target when the source and targets are far apart. As the organism becomes larger, the absorbed fractions increase, but because the mass is also increasing, the specific absorbed fractions (ϕ/m) for the fetus being irradiated by maternal organs at some distance do not increase greatly. However, these fractions exhibit sensitivity for nonpenetrating radiations such as alpha and beta particles.

As the fetal organs grow and begin functioning, they may selectively incorporate specific radionuclides or compounds. As was discussed above, the radiation dose to individual organs may change and the magnitude of the differences can become large. Although this occurs in several situations, a striking example is the dose to the fetal thyroid from radioactive iodine. The fetal thyroid does not preferentially incorporate iodine until the tenth week of gestation and so receives about the same radiation absorbed dose from radioactive iodine as do other tissues. However, after this time the fetal thyroid receives higher radiation doses than the remainder of the fetal tissues.

7.4.4 *Other Modifying Factors*

There is mounting evidence that genetic factors play an important role in determining metabolic characteristics (e.g., lipid deposition) of defined populations as well as of individuals (e.g., diabetic

susceptibility). Demonstrated placental transfer differences suggest that genetic factors are involved in differences among women in the availability of substances to their embryo/fetus.

Diet can play a major role in modifying the fraction of a radionuclide or a compound that is absorbed, incorporated and metabolized or organically bound by the woman and the fetus. These functions can be further influenced by medications. Similar relationships appear to pertain for other materials and drugs, but few of these relationships have been well defined.

Studies in experimental animals have quantified influences of alterations in uterine blood flow on the transfer of flow-limited materials across the placenta. Other experiments have shown effects of metabolic inhibitors on active transport. Damage to the yolk sac has been shown to affect transfer of material from the maternal circulation to the embryo/fetus in some species. Pathologic states that affect placental structural or function may be expected to have analogous effects on transfer.

8. Estimation of Embryo/Fetus Dose in Radiation Protection Practice

8.1 Operational Approaches

This Section suggests approaches to application of information from this Report and related documents to assessments of embryo/fetus dose in radiological protection practice. As evident from discussions in previous sections, the primary approaches to dosimetry when the subject is pregnant do not differ from standard assessment procedures for other purposes.

Unique aspects of dosimetric assessment for a pregnant woman may include different recommended or required dose limits and regulatory reporting requirements. These requirements may be expected to change with time and to differ among various operational environments. Additional considerations are that the target tissue usually is the embryo/fetus, or even specific tissues of the fetus, and that details differ with stage of gestation. Accordingly, the suggestions are best stated in general terms to accommodate these changes but discussions that relate to specific situations will be used for illustration.

8.1.1 Typical Situations

The most likely situations that would lead to a need for dosimetric evaluation of radionuclide intakes by pregnant women include: (1) dosimetry of radionuclide administration to patients, or accidents involving personnel in nuclear medicine; (2) establishing procedures for worker protection and compliance with operational rules and regulations in nuclear-related industries; and (3) dose calculations from radionuclide releases for the general population or for individual members as well as *post facto* estimates for epidemiologic evaluations associated with radionuclide releases to the

environment. Exposures may derive from single, multiple or chronic maternal intakes through various routes prior to or during pregnancy. Ingestion and inhalation are the most likely routes of intake, but injection is possible, e.g., in nuclear medicine.

Dosimetric needs and the selection of approaches to estimation of dose to the embryo/fetus usually will be guided by the uses that are to be made of the calculated or estimated dose rates and doses. The approach is also influenced by the amount of information available relative to the circumstances of exposure, including the specific radionuclides. As with any internal radionuclide deposition, evaluation should identify the radionuclides and their concentrations in the target tissue and in surrounding source tissues.

When combined with physical constants and conversion factors, information on body content and distribution gives energy deposition in the target tissue per unit time (dose rate) and integral dose (absorbed dose, dose equivalent, committed dose, etc.) when dose rates are integrated over time. The dosimetry still is based on the physical properties of the radionuclide and the characteristics of the emitted radiation but interactions may involve differences in physical dimensions, elemental composition, and density of the individual. As described in previous sections, pregnancy leads to changed biological conditions that include the size, shape, biokinetics and physiological processes as well as the presence of the embryo/fetus. Allowances for these differences have been incorporated into the methodologies and tabulations that are currently available for radiation dosimetry of the embryo/fetus.

8.1.2 *Characterization of Radionuclide in the Woman*

Radiation dose evaluations are based on identification of the radionuclides. In some situations, concentration or total content in organs and tissues of the woman and the embryo/fetus can be determined accurately. Under ideal conditions, calculations would relate the magnitude and period of body content to the stage of gestation during which the radionuclide was present. Other situations may require one or more assumptions for estimations of radionuclide burdens. In some instances, derived and secondary limits and approaches for assessment are available for use where incomplete information is available; alternatives appropriate to the situation should be applied.

8.1.3 Representative Scenarios

8.1.3.1 Nuclear Medicine Procedures. When radiopharmaceuticals are administered for nuclear medicine procedures, the radionuclide, its chemical form, and route of administration usually are known. The stage of gestation should be established and considered in making the decision whether to perform such procedures. The stage of gestation should be determined in case the pregnancy was not detected prior to the procedure.

8.1.3.2 Occupational Settings. Established procedures are used in the case of an accidental exposure or intake by a pregnant woman in an occupational setting. The radionuclide or radionuclides are usually known from the circumstances but analyses should be performed for verification or identification if necessary. The body content of the woman, including embryo/fetus, should be determined relative to the date(s) of exposure or intake using conventional measurements and calculations. Moreover, it is important that this information should be related to stage of gestation.

In such situations, repeated whole-body and specific organ counting may be employed. Indirect bioassay (urine or fecal assays) can be used for radionuclides or situations that are not amenable to *in vivo* measurements. The results of these assays should be evaluated in conjunction with biokinetic models of radionuclide transport to estimate initial deposition.

8.1.3.3 Delayed Detection of Exposure—Occupational or General Population. Alternative approaches are required for depositions of radionuclides in the body that are not detected until substantial time has elapsed after exposure. These involve determining the route of exposure and estimating the amount and time of intake of the radionuclides by the mother. The accuracy of such estimates differs with circumstances. Reconstructions of exposure conditions and amounts from historical information generally yield only rough approximations.

1. Ingested materials: The need is to determine the concentration, volume and fraction of ingested materials transferred to blood. An extensive tabulation of GI absorption factors (f_1) for radionuclides, which is applicable to most situations involving regulatory compliance, is given in an Appendix to 10 CFR Part 20 (NRC, 1991). Comparable values also are indicated in descriptions in Appendix A to this Report,

most of which are taken from ICRP Publications 56 and 67 (ICRP, 1989; 1993). These and subsequent publications give additional absorption and dosimetric factors.

2. Inhaled materials: The simplified approximation described in Regulatory Guide 8.36, which assumes instantaneous uptake into blood, is adequate for most situations involving inhalation exposures during gestation (NRC, 1992). This method allows for utilizing the differing general behavior of the lung clearance classes to determine activity in blood from inhaled activity. Values for radionuclides in selected chemical forms, as listed in Appendix B to 10 CFR Part 20, can be used to calculate transfer fraction (TF_1) as based on the equation for the class of radionuclide and the corresponding value of f_1 :
 - $TF_1 = 0.48 + 0.15 f_1$ for class D
 - $TF_1 = 0.12 + 0.51 f_1$ for class W
 - $TF_1 = 0.05 + 0.58 f_1$ for class Y

8.2 Prenatal Radiation Dose from Maternal Burdens or Intakes

8.2.1 *Information Sources to Facilitate Dosimetry*

In most situations associated with intake by a pregnant woman, the goal will be to determine the dose rate and/or the integral dose to the embryo/fetus. The concepts and methods described in Section 7 are most readily applied when body content, distribution and temporal factors can be determined. The dosimetry is facilitated when detailed information about placental transfer, biokinetics and/or dose factors for the radionuclides have been tabulated or are otherwise available. Essentially the same approaches are used for less well defined situations or radionuclides but estimations are required and accuracy may decrease.

Dosimetric databases and tables for the most frequently encountered radionuclides of many elements in relevant chemical compounds and forms are available in electronic or printed form. Identification of some information sources noted in descriptions of preceding sections will be repeated while reviewing representative situations. Use of appropriate databases, when available, facilitates estimation of dose rate or dose to the embryo/fetus. Selection of the specific approach depends on the pertinent conditions as well as local availability and personal preferences.

The personal computer software, MIRDOSE 3, was derived by applying MIRD methodology to age-related phantoms and to mathematical models of a woman at each trimester of gestation (C[h]risty and Eckerman, 1987; Stabin, 1996; Stabin *et al.*, 1995). Use of this program may prove to be of general applicability to obtain dose factors for a large number of radionuclides and self-dose and dose to target organs when values of residence time are available. In several instances, the tabulated target organs include the uterus or fetus, and apply to radionuclides in a wide range of source organs or dose from radionuclides in the entire woman.

8.2.2 Radiopharmaceuticals

The MIRD methodology (Section 7) currently is the most appropriate approach when radiopharmaceuticals have been administered to a pregnant patient and is generally applicable to accidental intakes. This methodology formalizes calculation of radiation dose to a target region from radioactive material in a source region. The two regions usually are distinct organs that are separated in space but the organs may be in the same region. In the case of the pregnant woman, the uterus and the embryo/fetus are considered to be the target regions and are also source regions. Other maternal tissues and the placenta, with related membranes, may be additional source regions.

Dosimetry of radiopharmaceuticals in patients is facilitated by the fact that intakes are generally well-characterized. Documents such as Loevinger *et al.* (1991) and ICRP Publication 53 (ICRP, 1987) give metabolic models and tabulations of dose factors for a comprehensive array of materials and for several tissues, including the uterus. Separate tables are provided for various medical conditions and interventions that affect biological disposition. In addition, a table of uterine dose factors that emphasizes specific uses of radiopharmaceuticals is available from the Swedish National Institute for Radiation Protection (STR, 1990).

Extension of these data to perform calculations for the appropriate trimester and distribution involves application of the MIRD formulas directly or use of the MIRDOSE 3 computer software. In other situations, the time course of radionuclide content would be measured and residence times calculated, based on uniform distribution or measured distribution in the body.

Currently, the most useful and comprehensive sources of tabulated dose factors are the publications of Russell *et al.* (1997a;

1997b), although it may be anticipated that similar materials will become available. These authors summarized organ residence times and developed estimates of placental transfer and dose for common radiopharmaceuticals that were combined with the biokinetic models from the Radionuclide Internal Dosimetry Information Center, the MIRDOSE program, and the approaches indicated above. This approach generated extensive dosimetric information and tabulations for the most frequently used radiopharmaceuticals in women of child-bearing age. Tables give absorbed dose estimates to the embryo/fetus per unit activity administered to the pregnant woman (mGy MBq^{-1}) for the maternal contribution to dose and for total dose including the self-dose contribution for radionuclides in the embryo/fetus. Separate values are given for doses at the four stages of gestation that they evaluated: early, three months, six months, and nine months. Another table was derived that includes an additional column presenting the quantity of radionuclide that is commonly administered in nuclear medicine procedures and gives the corresponding estimates of radiation dose to the embryo/fetus.

In practice, one would consult the appropriate table to obtain maternal contributions or the total radiation dose to the embryo/fetus corresponding to the specific nuclear medicine procedure and the prenatal age corresponding to the stage of gestation. One also could use data from these tables of retention times if it were desired to perform independent calculations or for verification.

8.2.3 Well-Characterized Intakes or Depositions

Most frequently, the ability to fully characterize the radionuclide deposition will be associated with occupational exposure situations. As indicated above, calculation of radiation dose to the embryo/fetus will be based on the amount of radionuclide that is determined to be in the pregnant woman and its fractional distribution in maternal tissues that serve as source organs, in the embryo/fetus, and the placental membranes. Multiplication of radionuclide content by appropriate dose factors yields estimates of radiation absorbed dose rate and dose during relevant times of gestation.

In practice, convenient approaches that are acceptable for compliance with many regulatory needs can be based on descriptions and tabulations for several occupationally relevant radioactive materials given in Regulatory Guide 8.36 (NRC, 1992) and

expanded in NUREG/CR-5631 (Sikov and Hui, 1996). These documents give tables of gestational-age-related values of fractional deposition and retention in the embryo/fetus for a bolus of radionuclide that has been intravenously injected in a pregnant woman. Multiplication of the woman's content by the fractional deposition yields the quantity of radionuclide initially deposited in the embryo/fetus and the amount remaining at subsequent times.

These quantities could be multiplied by dose factors to obtain radiation dose rates and doses at the relevant times of gestation. This determination often can be facilitated by use of another series of tables that were generated for these documents. For each of the deposition/retention fractions, corresponding to the month of gestation at intake and time after administration, self-dose rates were calculated and added to the radiation dose contribution from a radionuclide in maternal organs. The calculated radiation dose rates were integrated to obtain monthly doses to the embryo/fetus corresponding to intravenous administration of a nominal 37 kBq bolus. NUREG/CR-5631 (Sikov and Hui, 1996) gives tables of dose factors (dose equivalent) at monthly intervals, or more frequently for short-lived radionuclides, and dose through the remainder of the pregnancy. In practice, these factors are multiplied by the estimated content of radionuclide in maternal blood following intake to obtain radiation dose rates and doses.

8.2.4 *Incompletely Characterized Radionuclides or Depositions*

8.2.4.1 Concentration Ratios. Data concerning relative maternal distribution varies among radioactive materials. Data for some radionuclides are not sufficient to develop even simple dose factor tabulations. The reported data sometimes have been converted to ratios of the activity in or radiation doses to the embryo/fetus compared to the activity or dose to the woman or her organs. Information is sometimes available from which extrapolations of relative concentrations can be derived.

Thus, for some radionuclides the comparison is to specific maternal organs, for others the maternal reference is her whole body, and radiation dose ratios have been reported in still other situations. Moreover, fetal or fetal organ to maternal organ concentration ratios or radiation dose ratios are sometimes available; these ratios may provide a basis for population-related estimates (Roedler, 1987; Stather *et al.*, 1987). The table of values for rutherfordium given in Appendix A serves as an example of this approach.

8.2.4.2 Uterine Surrogate. There will be situations in which the amount of radioactive material in the woman's tissues can be assessed but placental transfer information is not available. As described in Section 7 and in this Section, tabulation of dose factors for the uterus are readily available for many radionuclides and chemical forms. The doses calculated from such tabulations provide good estimates for embryonic stages but are less-valid approximations of radiation dose at later stages of fetal development. These estimates of dose to the embryo/fetus, however, currently are appropriate for many regulatory purposes that accept the uterus or uterine contents as a surrogate target tissue (NRC, 1992).

8.2.4.3 General Estimates. Many of the descriptions of radioelements in Appendix A of this Report include biokinetic models that report deposition and retention in the embryo/fetus. Typical dosimetric results from the literature, as well as representative values or ranges of values from dose factor tables, can be used in situations where detailed estimates of dose are not required. These models or values are sometimes used as a basis for extrapolations to obtain estimates for other isotopes of these elements by adjusting for differences in emissions and half-lives.

8.3 Secondary Evaluations and Derived Limits

In some situations, known inaccuracies in the estimates of intake, body content, time of exposure, and stage of gestation prevent calculation of detailed dosimetry. The summarized values of dose rate or integrated dose given for some of the radionuclides in Appendix A can be used to provide acceptable approximations when less detailed estimates of dose are required. Typically, such approaches would relate to epidemiological evaluations, especially in the case of intakes by members of the general population.

Several surrogate and derived estimators and limits have been established to facilitate compliance with regulatory requirements. Most commonly, these may accommodate situations that are facilitated by demonstrating that radiation dose is expected to be less than given fractions of the relevant limit so as to obviate the need for more detailed dosimetry or control measures.

A general example of the concept is inherent in the regulations of the NRC and the recommendations of the ICRP and the NCRP that address this situation by reference to intakes by adults. As a

general expectation, in most scenarios that involve intakes of radionuclide prior to or during pregnancy, the internal doses to the embryo/fetus are related to maternal intake. In turn, intakes are restricted in terms of secondary limits or reference levels such as the ALI given by the ICRP (1991) or the ARLI given by the NCRP (1993). Accordingly, recommended control levels often are given relative to fractions or multiples of ALI or ARLI so that dose factors that provide these relationships facilitate calculations.

Other operational needs may involve requirements to restrict intakes to levels that lead to cumulative radiation doses to the embryo/fetus that are not likely to exceed specified values. Tables of such relationships provide a basis for estimating radiation doses to the embryo/fetus from maternal intakes of radioactivity and are also useful for epidemiologic evaluations. These approaches are discussed in NRC (1992) and Sikov and Hui (1996). A series of associated tables were developed on the basis of the values of ALI and fractional absorption factors given in Appendix B to 10 CFR 20 (NRC, 1991). The approaches in these documents are briefly reviewed in the following paragraphs as examples but relate specifically to the indicated values of ALI. Other definitions and values of ALI can be used in an analogous manner when appropriate.

8.3.1 Use of Uterine Dose as Surrogate

The use of radiation dose to the nonpregnant uterus or uterine contents at selected gestational stages as surrogates for the embryo/fetus was discussed in forgoing paragraphs of this Section. As indicated, calculated values of radiation dose are tabulated in several sources. In addition, Sikov and Hui (1996) used formalized values of absorption factors and inhalation classes relative to intake of an ALI of various physicochemical forms of several radionuclides to calculate and tabulate nominal uterine radiation doses. The tables in NUREG/CR-5631, Rev. 2 (Sikov and Hui, 1996), give dose per ALI, fractional ALI, and activity for 0.5 mSv.

8.3.2 Dose to the Embryo/Fetus and ALI

Results of calculations for common physical and chemical forms of occupationally important radionuclides have been tabulated in terms of radiation doses to the embryo/fetus that result from an ALI (Sikov and Hui, 1996). These tables give intake levels that result in 0.5 mSv to the embryo/fetus and are expressed as fraction of an ALI and activity as well as the reciprocal values for other

control purposes. That report gives other tables with results of similar calculations to obtain surrogate dose approximations that are based on values of committed dose equivalent to the uterus.

8.3.3 *Depositions Before Pregnancy*

Sometimes there is a need to obtain estimates of nominal doses to the embryo/fetus from radionuclide burdens incurred by the woman before pregnancy. The maximum dose often would be calculated through use of an assumption that the woman's total body content immediately before pregnancy was transferred to her blood at the time of conception. Nominal values of radiation dose through gestation have been tabulated on the basis of a burden that corresponded to an ALI and the above-indicated derived tables of radiation dose to the embryo/fetus relative to ALI (NRC, 1992; Sikov and Hui, 1996). Based on the actual burden as a fraction of ALI and the corresponding entry in the table, a nominal dose can be calculated. This simplified approximation, which is described in Regulatory Guide 8.36, will be adequate for most situations involving radionuclide deposition in a woman prior to her pregnancy (NRC, 1992).

8.3.4 *Chronic or Multiple Intakes*

Approaches are often required for evaluating multiple radionuclide intakes during gestation. The ALI approach has been extended to provide tabulations of the estimated amount of radioactive material that enters the transfer compartment from repeated or chronic exposures through all or significant fractions of gestation. In these calculations, chronic exposures are approximated by a series of intakes corresponding to one-ninth ALI at the beginning of successive 30 d periods of pregnancy and then multiplying the sequential intakes or burdens by appropriate conversion factors to obtain amounts in the transfer compartment. The reports describing the methods and giving the tables may be consulted when such determinations are needed (NRC, 1992; Sikov and Hui, 1996).

9. Research Needs

Several caveats and limitations were discussed in foregoing sections to emphasize that greater certainty should not be attached to patterns and estimates than is warranted. This Section identifies areas for research and concept development that should resolve some of the uncertainties.

9.1 Additional and More Adequate Data

Only limited quantitative information about placental transfer and distribution of nuclides are available from human experience. The accuracy of dosimetric models and calculations continue to be related to the validity of extrapolations from animal data to humans. Additional data from experiments with nonhuman primate species for confirmation and validation would increase confidence in conclusions and models or could lead to needed revisions. There is a need for development of formal strategies for enhancing extrapolations. Expansions and validation using physiologic information and biokinetic modeling are needed to maximize the usefulness of current information as well as additional information that might be identified later.

9.2 Development of Concepts and Procedures

9.2.1 Extrapolation and Chronicity Problems

Essentially all transfer between the pregnant woman and the fetus takes place across the placenta *via* their blood circulations. Neither single, sets, nor series of expressions have been validated for placental transfer that would be comparable to the f_1 parameters that are used to denote fractional absorption of materials from the GI tract. Such fractional transfer values could be useful, but the approach poses difficulties because many fractions would

change throughout gestation. Tentative transfer fractions pertaining to broad periods of gestation have been estimated for common compounds of several elements and these values have been compared with the corresponding f_1 values for GI and pulmonary absorption (Sikov *et al.*, 1992a). More formal strategies are needed so that, as further information is obtained, additional elements and compounds could be addressed. Allowances should be defined to integrate stage-dependent patterns and kinetics as well as to incorporate the role of relevant target tissues and their metabolic capacities.

Radionuclide exposure of the human conceptus might be generally categorized as resulting from burdens in a woman before pregnancy, from chronic or multiple low-level intakes by a pregnant woman associated with contamination, or from single incidents that result from an accidental or purposeful administration. These exposure scenarios require different approaches to evaluate, both from the metabolic and the dosimetric standpoints. Modeling of kinetics to reach conclusions from animal experiments requires consideration of the impact of gestational stage on the fraction of the radioactivity that is transferred per incremental time period and on the fetoplacental distribution pattern. The lack of complete correlations among results of analyses of human materials after differing exposure patterns, as well as their relationships to animal data, indicate a need to explain the basis for differences. In particular, rational hypotheses must be developed to integrate the interactions that underlie differences relating to exposure conditions and among species.

9.2.2 Nonuniform Fetal Deposition

There are theoretical difficulties with using localized radioactivity to calculate average radiation doses throughout the fetus. This situation is not consistent with current recommendations regarding radiological protection (ICRP, 1991a; NCRP, 1993; NRC, 1991). From a practical standpoint, however, a basis has not been established for using the local radiation doses to fetal organs or tissues for radiation protection. It is obvious that analyses, recommendations and decisions about dosimetric approaches and the use of results are necessary.

The major dosimetric impact of localized activity is illustrated by radioiodines in the fetal thyroid gland, an example that is provided in the Appendix. From the standpoints of radiosensitivity and the potential for late effects, there are analogous needs for

radionuclides that have skeletal distribution patterns and those with marked extraembryonic deposition. Moreover, soft tissues are irradiated and may be affected by radionuclides deposited in nearby bone.

Because of demonstrated differences in relative tissue responsiveness, derived expressions that are used for control of radiation exposure in adults are not appropriate for the embryo/fetus. In addition to the errors in assignment of w_T , this problem requires consideration and resolution from the dosimetric standpoint, as noted in the previous paragraph. The uncertainty assumes even greater relevance when microdosimetric and stoichiometric aspects are included.

9.2.3 *Extraembryonic Deposition*

Some radioactive materials such as thorium, especially as Thorotrast®, deposit in the placenta, restricting its entry into the fetus. Others, such as actinides, deposit in both the chorionic and yolk sac placentas, as well as in the fetus to a lesser extent. Because the progenitor cells of the gametes and hematopoietic lines appear initially in blood islands of the yolk sac, the possibility has been suggested that selective irradiation of these primitive stem cells may be related to reported clusters of leukemia. Data apparently have not been reported to suggest that such exposures of rodents, even at high levels of administered activity, lead to delayed effects such as inhibition of reproductive function, premature decline of the hematopoietic system, or increased incidences of neoplasms of blood-forming tissues. The possibility of these interactions may require consideration in evaluating the dosimetry of these nuclides and potential detrimental effects on structure and function.

10. Summary and Conclusions

Radionuclides may enter a woman under various circumstances including occupational exposures, medically related administrations, or intake from the general environment. This Report addresses the determination of radiation dose to the embryo/fetus from radionuclides that are present in a woman before her pregnancy or that enter during pregnancy. These doses may be the sum of those attributable to the radionuclides in the maternal system plus those that are transferred into the placenta or other membranes, the embryo/fetus, and the fetoplacental fluids.

The transfer of radioactivity from the pregnant woman to the fetoplacental system, the distribution of the activity, and the developmental effects of the resulting radiation absorbed doses are all affected by gestational stage. For these reasons, the anatomical and physiological development of the embryo/fetus are reviewed and a synopsis of radiation effects is presented for representative periods of prenatal development with emphasis on those effects resulting from internally deposited radionuclides. Because much of the knowledge regarding placental transfer and radiation effects on the human embryo/fetus is based on extrapolation of data from animals, information is provided on the comparative development of species that most commonly have been used in experimental studies.

Calculation of radiation absorbed doses to the embryo/fetus and its individual tissues or organs is complicated by the continuously changing anatomical and physiological characteristics during intrauterine development. These complications also affect the models and calculations of the kinetics of transfer of radioactivity between the maternal and fetoplacental systems. Absorbed doses from alpha and beta particles as well as secondary electrons with photon radiation are affected by the small sizes of structures, organs or tissues of the embryo/fetus, which often have dimensions less than the path length of the particles.

Little or no information is available concerning transfer to the placenta or embryo/fetus for many radioactive compounds that

may enter the maternal system. Much has been learned from experimental studies with animals, but this database also is incomplete and interspecies differences make the validity of extrapolations uncertain. Direct human studies, including evaluation of accidental exposures, should be considered to the extent permitted by legal and ethical considerations.

APPENDIX A

Selected Physical and Biological Data — By Element

This Appendix presents information about individual elements or series of elements, usually in order of atomic number. The isotopes and compounds of primary interest have been identified, especially those that may be of interest relative to the embryo/fetus. Brief comments only are given for elements that do not have isotopes or properties that were considered relevant to radiation dosimetry during pregnancy.

Whenever possible, the general biological models have been based on descriptions given in ICRP Publications 56 and 67 (ICRP, 1989; 1993) but the models of Publications 23 and 30 (ICRP, 1975; 1979) were used when needed. The sources for models are not specifically cited repeatedly and have been supplemented through information given in original reports as well as in compendia and in other analyses and summaries.

To the extent necessary, information was taken directly from reviews and syntheses by others and has been used, without confirmation, in the following descriptions. The text indicates when no relevant reports about disposition during pregnancy were located or where minimal information was found.

Examples are provided to illustrate approaches to calculations of radiation absorbed dose from these descriptions. Calculations were performed for iron, gallium, cesium and iodine and the results are included with their descriptions. References to and/or results from other estimates of radiation dose are also provided, when applicable. A discussion of these approaches to calculations and estimation is given in Section 7 of this Report.

General guidelines were described in Section 8 for use in radiation protection situations in which there is the absence of adequate

information. When the concentration in the embryo/fetus is less than that of the mother and there is no known tissue localization, it may be assumed that the radiation dose is no greater than that to the mother.

A.1 Hydrogen

Hydrogen (H , $Z = 1$) has three isotopic forms; two are stable, 1H and 2H , and one is radioactive, 3H . The radioactive isotope, usually referred to as tritium, emits an 18.6 keV beta particle and has a half-life of 12.3 y. Tritium is generated in nuclear reactors but also is present naturally because of continuous production by the reaction of fast neutrons in cosmic rays with atmospheric nitrogen (Moghissi and Carter, 1973).

A.1.1 *Biological Information*

Stannard (1988) gives a concise review of the properties and status of biochemical research involving tritium. Tritium is readily absorbed from the lung or GI tract ($f_1 = 1$) when present as a gas or in water molecules. Further discussions of the metabolism of various tritium-labeled compounds are presented in ICRP Publications 30 and 56 (ICRP, 1979; 1989) and in NCRP Reports No. 62 and No. 63 (NCRP, 1979a; 1979b). Although tritium has relatively low general toxicity, it has been of concern because of the large amounts that are produced both in fission and in fusion reactions so that release to the environment could result in significant exposures (Dobson, 1979).

Tritium has been used to label a wide variety of organic compounds, in particular thymidine, cytidine, uridine, vitamins, estrogens, amino acids, and purines. Thymidine is particularly interesting because it is normally found only in the cell nucleus. Tritiated thymidine can be used to label chromosomes, and in this form is used in studies of cell reproduction.

Because its atomic weight is three times that of 1H , an isotopic effect occurs in some reactions involving tritium. In particular the specific activity of tritium in the water in expired air is lower than that in plasma. With chronic exposures, this could lead to a higher radiation dose than would be calculated from a single acute exposure (Robertson, 1973).

A.1.2 Fetal/Placental Information

The biokinetics and the radiation dose from tritium to the embryo/fetus are highly dependent on the administered form. The most common form in which tritium enters the body is as labeled water, HTO. In this form it has a biological half-life of about 10 d in the adult and in the embryo/fetus. Measurements indicate that it rapidly exchanges throughout the total body water, and in fact is used to measure total body water in body composition studies. In particular, it is readily exchanged between the woman or pregnant animal, the placenta, and the embryo/fetus (Meschia *et al.*, 1967; Neslen *et al.*, 1954).

A small fraction of tritium that enters the body exchanges with the hydrogen in organic compounds. In this form, it may persist in the body for relatively long times; exponential components with halftimes up to 300 d have been observed. Many organic metabolites such as glucose and amino acids readily enter the placenta and their metabolism is similar to that in the woman. About one-half of glucose or amino acids entering the fetus is incorporated into glycogen or protein, respectively, and is retained with a halftime of about 50 d. The other one-half is considered to be catabolized to water within a day. Tritiated water in the embryo/fetus, whether entering as such or formed by catabolism, is assumed to be retained with the same 10 d halftime as in the woman.

A comprehensive review of earlier studies of the effects of tritium on rat embryos and fetuses is given in a book by Moskalev (1968). Disturbances in the development of offspring both in the period of prenatal life and in the postnatal period were noted. Newborn rats showed various anomalies of development, including weak respiration, smaller body size, edema and pathological changes in the vascular system.

In experiments with mice, Torok *et al.* (1979) found that with single injections of 2.6 MBq of tritium per gram of body weight for dams on day nine postconception, the offspring showed significantly decreased weights for brain and genital tract organs. Injection of 20 MBq g⁻¹ caused perinatal mortality in 100 percent of offspring.

Cahill *et al.* (1975; 1976) maintained pregnant rats at constant body activities of tritiated water throughout pregnancy. They used quantities that ranged from 37 to 3,700 kBq mL⁻¹ of body water and yielded doses of 3 to 300 mGy d⁻¹ to the embryo/fetus. Biological effects included microencephaly, sterility, stunting, litter size reduction, and increased resorption. Tritium incorporation into

fetal organs was 20 to 30 percent of the average maternal water concentration during gestation.

Using models similar to those described above, Sikov and Hui (1996) estimated radiation absorbed doses and dose rates for tritium as water or as representative organic compounds for different periods after injection into the mother's blood at one of several stages of gestation. Dose rates were reported to vary among gestational stages but the cumulative doses through the remaining gestation were roughly $0.18 \text{ mGy kBq}^{-1}$ for tritiated water and ranged from 0.19 to $0.32 \text{ mGy kBq}^{-1}$ for typical organic forms.

A.2 Helium

Helium (He , $Z = 2$) has two stable isotopes, ^3He and ^4He . It also has three radioactive isotopes, ^5He , ^6He and ^8He , all of which have half-lives less than 1 s.

Helium is more soluble in lipids than in water and therefore tends to concentrate in fatty tissues. When inhaled stable helium produces interesting physiological effects, such as altered pitch of voice. Its radioisotopes are not of concern to radiation protection.

A.3 Lithium

Lithium (Li , $Z = 3$) has two stable isotopes, ^6Li and ^7Li . It has four radioisotopes, ^5Li , ^8Li , ^9Li and ^{11}Li , each with a half-life less than 1 s.

Stable lithium is a demonstrated teratogen in rodents. Characteristic cardiovascular anomalies have been found in children born to women receiving lithium therapy (Shepard, 1992).

Placental transfer was studied in dogs using stable lithium carbonate administered by injection and infusion over a 2 h period (Hugher *et al.*, 1973). They did not detect lithium in fetal blood when maternal blood levels were below 3 to 5 mEq L^{-1} but transfer was measured at higher concentrations, up to 50 mEq L^{-1} . Administration of lithium in drinking water increased plasma concentrations in pregnant mice but concentrations in fetal plasma were about one-half of those values. Brain lithium did not differ between the adult and fetus but fetal bone concentrations were lower (Smithberg *et al.*, 1984).

A.4 Beryllium

Beryllium (Be, Z = 4) has one stable isotope, ^{9}Be . Its radioisotopes include ^{7}Be (half-life 53.3 d), ^{10}Be (half-life 1.6×10^6 y), ^{11}Be (half-life 13.8 s) and three others, ^{6}Be , ^{8}Be and ^{12}Be , with half-lives less than 1 s.

The absorption of beryllium from the GI tract (f_1) is considered to be 0.005. The fractional absorption of beryllium entering the body by inhalation also is estimated to be 0.005. There are moderate and long-term components of beryllium retention in the lung depending on the compounds (ICRP, 1981).

Available data suggest that the skeleton is likely to contain most of the body's beryllium (ICRP, 1981). After absorption into the blood, beryllium is predominantly deposited and retained in bone (Furchner *et al.*, 1973) although in the first few days after intravenous injection of the sulphate the liver and spleen contain high concentrations of the element. For dosimetry it is assumed that of the beryllium leaving the blood, 40 percent is translocated to mineral bone, 20 percent is uniformly distributed throughout the rest of the body, and the remainder is assumed to go directly to excretion (ICRP, 1981).

Beryllium translocated to bone is assumed to be retained with a biological half-life of 1,500 d. For dosimetry purposes ^{7}Be and ^{10}Be are assumed to be uniformly distributed throughout the volume of mineral bone at all times after their deposition. In organs or tissues other than skeleton, fractions of 80 percent and 20 percent are assumed to be retained with biological half-lives of 15 and 1,500 d, respectively.

No data were located concerning the placental transfer of beryllium or its biological behavior in the embryo/fetus.

A.5 Boron

Boron (B, Z = 5) has two stable isotopes, ^{10}B and ^{11}B , and five radioisotopes, ^{8}B , ^{9}B , ^{12}B , ^{13}B and ^{14}B , each with half-life less than 1 s.

Boron is prevented by the blood-brain barrier from entering the brain of normal adults. However, ^{10}B has been used in experimental neutron capture therapy of brain tumors.

Pregnant women have not been treated by this method so that no information has become available. There is inferential evidence for placental transfer of stable boron, as borax or boric acid, however, based on teratologic effects (Shepard, 1992).

A.6 Carbon

Carbon (C, Z = 6) has two stable isotopes, ^{12}C and ^{13}C , and six radioisotopes, ^9C , ^{10}C , ^{11}C , ^{14}C , ^{15}C and ^{16}C . ^{14}C , with a half-life of 5,730 y, occurs in nature and is widely used in procedures such as carbon-dating of ancient substances. ^{11}C , a positron emitter with a half-life of 20.3 min, is particularly useful in imaging studies performed with positron emission tomography.

A.6.1 Biological Information

Radiocarbon can enter the body in inorganic forms such as the gases CO and CO_2 , and other compounds such as carbonates. It also can enter in a wide variety of organic compounds, including many of metabolic importance. The fractional GI absorption for all forms is considered to be one (ICRP, 1989) but distribution kinetics depend upon the chemical form in which it enters the body.

A.6.2 Fetal/Placental Information

Glucose is actively transported from maternal to fetal blood across the placental layers, uterine blood, and then to the umbilical circulations and fetus. The concentration gradient between glucose in maternal and in fetal blood serves as a major driving force for its placental transfer. The most substantial quantitative data are available from studies of pregnant sheep; the general patterns are consistent with information from other species, including humans (Battaglia and Meschia, 1978; Hay and Meznarich, 1989; Meschia, 1983). Using the positron-emitting ^{11}C , Ishiwata *et al.* (1985) studied the placental transfer of metabolic substrates and analogs such as sugars, amino acids, adenine, adenosyl-L-methionine and coenzyme Q in pregnant rats. Much higher uptakes of these substances were found in the fetal brain than in the maternal brain (also see fluorine).

The overall glucose utilization rate per gram of tissue is higher in the fetus than in the pregnant female. During late gestation, consumption of glucose by the uterus and its contents represents 30 percent of the total maternal glucose utilization. Of this amount, 60 percent of the net glucose uptake is consumed by the placenta and 40 percent is utilized by the fetus. In fetal lambs, approximately 60 percent of uniformly labeled ^{14}C glucose infused to the fetus is oxidized to $^{14}\text{CO}_2$. As compared to the fetal lamb, the human fetus is characterized by a higher ratio of brain/fetal

weight, more efficient placental glucose transfer, and a higher proportion of fat (16 percent versus 2 percent at term). The $^{14}\text{CO}_2$ produced in the fetal catabolism of glucose does not accumulate in the fetus, but is excreted to the mother *via* the placenta and then exhaled.

Only trace amounts of fructose are present in human blood. It is assumed that negligible amounts of this and other hexoses are transferred to the fetus.

Most amino acids are actively transported across the placenta in both directions. In general the concentrations of free amino acids in fetal tissues are similar to those in maternal tissues. Amino acids serve as metabolic components for the synthesis of proteins and are oxidized to provide energy. Significant amounts of labeled amino acids are incorporated into protein during organogenesis and the growth phases of gestation. The concentration is subsequently reduced through dilution during progressive growth. Although small amounts of ^{14}C may enter the carbohydrate pool after oxidation, the predominant fraction will be rapidly excreted as $^{14}\text{CO}_2$ and does not make a significant contribution to the radiation dose.

Sikov and Hui (1996) presented tables of estimated radiation absorbed doses and dose rates for ^{14}C as representative organic compounds introduced into the mother's blood at several stages of gestation and for different periods after intake. Initial dose rates did not differ greatly with administration times and sequential cumulated doses during the remainder of gestation amounted to about 0.03 to 0.05 Gy for injection of 37 kBq at any time during the fetal period.

A.7 Nitrogen

Nitrogen (N, Z = 7) has two stable isotopes, ^{14}N and ^{15}N , and six radioisotopes. One radioisotope, ^{13}N , has a half-life of about 10 min and the other five, ^{12}N , ^{16}N , ^{17}N , ^{18}N and ^{19}N have half-lives of less than 1 s.

Dry air is about 78 percent gaseous nitrogen by volume, but nitrogen is found as a component of protein and other biologically important organic molecules. The biological half-life of nitrogen is 90 d for soluble compounds such as ammonium salts, cyanides and nitrates.

A.8 Oxygen

Oxygen (O, Z = 8) has three stable isotopes, ^{16}O , ^{17}O and ^{18}O , and six radioisotopes, ^{13}O , ^{14}O , ^{15}O , ^{19}O , ^{20}O and ^{21}O . Dry air contains about 21 percent oxygen by volume as O_2 . The concentration of CO_2 in air varies between 0.01 and 0.1 with an average of about 0.033 percent by volume.

A.8.1 Biological Information

Oxygen is essential to metabolism in all animals, including humans. It is transported in the blood from the lungs to other tissues by combining with hemoglobin in the lungs and is released in exchange for carbon dioxide in the tissues. Water labeled with ^{15}O has been used in tracer studies.

A.8.2 Fetal/Placental Information

Oxygen and carbon dioxide, as the gases, rapidly cross between the maternal and fetal circulations (Metcalf *et al.*, 1967). Reneau *et al.* (1974) gives a theoretical analysis of the dynamics of oxygen exchange.

Goplerud and Delivoria-Papadopoulos (1985) discuss the role of the placenta in effecting gas exchange between the fetal and maternal circulations. Among the differences between fetal blood and adult blood characteristics is that fetal blood hemoglobin has a higher oxygen affinity than that of adult blood.

A.9 Fluorine

Fluorine (F, Z = 9) has one stable isotope, ^{19}F , and eight short-lived radioisotopes, ^{15}F to ^{18}F and ^{20}F to ^{23}F .

A.9.1 Biological Information

Absorption of fluoride from food or water is rapid and essentially complete ($f_1 = 1$). Fluorine entering the blood is very rapidly deposited in mineral bone (ICRP, 1980).

A.9.2 *Fetal/Placental Information*

Fluorine-18, a positron emitter with a half-life of 109.8 min, has been used to study the placental transfer of ^{18}F -2-deoxy-2-fluorodeoxyglucose and ^{18}F -5-fluorodeoxyuridine in pregnant rats (Ishiwata *et al.*, 1985). As in studies of ^{11}C -labeled sugars and amino acids, higher concentrations were found in the fetal brain than in the maternal brain. Bawden *et al.* (1964) studied the placental transfer of ^{18}F in sheep.

A.10 Neon

Neon (Ne, Z = 10) has three stable isotopes, ^{20}Ne , ^{21}Ne and ^{22}Ne , and six radioisotopes, ^{17}Ne , ^{18}Ne , ^{19}Ne , ^{23}Ne , ^{24}Ne and ^{25}Ne , with half-lives ranging from a fraction of a second to 3.38 min. Neon is an inert gas with no soluble compounds.

A.11 Sodium

Sodium (Na, Z = 11) has one stable isotope, ^{23}Na . It has 16 radioisotopes, ^{19}Na to ^{22}Na and ^{24}Na to ^{35}Na . Of these, ^{22}Na (half-life 2.6 y) and ^{24}Na (half-life 14.97 h) are most significant in radiation dosimetry.

A.11.1 *Biological Information*

Sodium compounds are considered to be completely absorbed from the GI tract and are assigned an f_1 value of one. It is a natural component of intracellular and extracellular fluids where it is present in ionic form. About one-third of the sodium in the body is found in the skeleton (ICRP, 1980).

The biological half-life of sodium is strongly influenced by the level of stable sodium in the diet. For dosimetry, the ICRP (1980) assumes that 30 percent of sodium leaving the transfer compartment (blood) is translocated to the skeleton. The remainder of sodium leaving the transfer compartment is assumed to be uniformly distributed throughout all other organs and tissues of the body.

A.11.2 Fetal/Placental Information

Neslen *et al.* (1954) calculated that sodium exchanges between the amniotic fluid and the maternal system at the rate of 0.014 moles h⁻¹, based on studies in two pregnant women at term. Both ²²NaCl and ²⁴NaCl have been used to study the placental transport of sodium in the guinea pig (Stulc and Svhovec, 1977). Friedman *et al.* (1959) studied the exchange of water and sodium in the amniotic fluid of pregnant monkeys. The data were analyzed using two and three compartment models.

A.12 Magnesium

Magnesium (Mg, Z = 12) has three stable isotopes, ²⁴Mg, ²⁵Mg, ²⁶Mg and 10 radioisotopes, ²⁰Mg to ²³Mg and ²⁷Mg to ³²Mg. The most significant radioisotopes for dosimetry are ²⁷Mg (half-life 9.45 min) and ²⁸Mg (half-life 21.0 h).

A.12.1 Biological Information

It was noted by the ICRP (1981) that the fractional absorption of dietary forms of magnesium vary from 0.14 to 0.7, depending upon the level in the diet, but assigned an f_1 value of 0.5. Stable magnesium is concentrated in mineral bone.

Studies in humans (Roessler, 1972; Silver *et al.*, 1960; Yun *et al.*, 1966) indicate components of retention of magnesium with biological half-lives of between 0.25 and 35 d. For dosimetry it is assumed that of magnesium leaving the blood, 20 percent goes directly to excretion, 40 percent to mineral bone, and 40 percent is uniformly distributed throughout the rest of the body. In all tissues the biological half-life is assumed to be 100 d. For isotopes with radioactive half-lives of 1 d or less, it is assumed that magnesium is uniformly distributed over the surface of mineral bone at all times following its deposition in that tissue.

A.12.2 Fetal/Placental Information

Studies with pregnant dogs indicate that magnesium does not enter the fetal circulation rapidly (Hugher *et al.*, 1973). Increased concentrations of magnesium in the maternal blood did not result in increased concentrations in the fetal blood in a 2 h experiment.

A.13 Aluminum

Aluminum (Al, Z = 13) has one stable isotope, ^{27}Al . It has nine radioisotopes, ^{22}Al to ^{26}Al and ^{28}Al to ^{31}Al , with half-lives ranging from fractional seconds to years.

The fractional absorption of aluminum from the GI tract is assigned a value of 0.01 (ICRP, 1981). The concentration of stable aluminum is greater in the lungs and skeleton than in the remainder of the body (ICRP, 1975). The high concentration in the lungs may be due to inhalation of aluminum. In rats, ^{28}Al intravenously injected as the chloride was rapidly taken up by the liver (Kushelevsky *et al.*, 1976), but in rats fed a diet containing one percent $\text{Al}_2(\text{SO}_4)_3$ the element was concentrated only in the skeleton (Berlyne *et al.*, 1972). The result with the chloride was probably due to the formation of an insoluble colloid.

For dosimetry it is assumed that of the aluminum leaving the blood, 30 percent is translocated to mineral bone and 70 percent is uniformly distributed throughout the rest of the body. In all tissues it is assumed to be retained with a biological half-life of 100 d. It is assumed that in the skeleton aluminum isotopes are uniformly distributed over bony surfaces at all times following their deposition in mineral bone.

No reports of studies involving intakes during pregnancy were found.

A.14 Silicon

Silicon (Si, Z = 14) has three stable isotopes, ^{28}Si to ^{30}Si , and eight radioactive isotopes, ^{24}Si to ^{27}Si and ^{31}Si to ^{34}Si . With the exception of ^{32}Si , which has a half-life of about 100 y, all of the radioisotopes have half-lives of less than 1 d.

Limited data indicate that most of stable silicon is uniformly distributed throughout the body. High concentrations are found in the lungs and thoracic lymph nodes because of inhalation of siliceous dusts (ICRP, 1981). Animal studies indicate that the absorption of dietary silicon from the GI tract is of the order of 0.003 to 0.03. The value for f_1 is considered to be 0.01, although studies in humans indicate that the fractional absorption may be as much as 0.5 when silicon is ingested as part of a low fiber diet (Kelsay *et al.*, 1979).

For dosimetry it is assumed that silicon leaving the blood becomes uniformly distributed in all organs and tissues of the body. Of silicon deposited in any organ or tissue, fractions of 0.4 and 0.6

are assumed to be retained with biological half-lives of 5 and 100 d, respectively.

No reports of studies involving pregnancy were located.

A.15 Phosphorus

Phosphorus (P, Z = 15) has one stable isotope, ^{31}P , and nine radioisotopes, ^{26}P , ^{28}P to ^{30}P and ^{32}P to ^{36}P . Other than ^{32}P and ^{33}P , which have half-lives of 14.38 and 25.3 d, respectively, the half-lives are less than 3 min.

A.15.1 Biological Information

Phosphorus is an essential element, forming an integral component of the structure and chemistry of protein, DNA and bone. The daily intake is considered to be 1.4 g and the body content is 750 g [50 g in muscle and 700 g in skeleton (ICRP, 1975)]. Models for the distribution and retention of soluble phosphorus consider that dietary phosphorus is absorbed from the GI tract with an f_1 of 0.8 (ICRP, 1979; 1987). Phosphorus entering the blood plasma is assumed to be retained there with a biological half-life of 12 h. Of this, 15 percent goes directly to excretion, 15 percent goes to intracellular fluids and is retained with a half-life of 2 d, 45 percent goes to soft tissue and is retained with a biological half-life of 19 d, and 30 percent goes to mineral bone (15 percent to each of cortical and cancellous bone) where for dosimetric purposes it is assumed to be permanently retained. Stable phosphorus is uniformly distributed in mineral bone. For dosimetry purposes, ^{32}P and ^{33}P are assumed to be uniformly distributed in mineral bone, and the shorter-lived isotopes are assumed to be retained on bone surfaces.

A.15.2 Fetal/Placental Information

Studies in rats found that phosphate readily crosses the placenta but that the transfer of phospholipid is much slower (Nielson, 1942). Experiments yielded consistent results in guinea pigs (Wilde *et al.*, 1946), sows (Newland *et al.*, 1960), and rats (Sikov, 1961). The overall pattern is that relative concentrations in the embryo/fetus increased as the ^{32}P was administered at progressively later stages of gestation and that rapidity of reaching maximum activity and retention followed the same pattern.

Watson *et al.* (1992) and Sikov and Hui (1996) derived general operational models of prenatal distribution for calculating the self-dose to the embryo/fetus by extrapolating the pattern from animal experiments. At one and three months of gestation (*i.e.*, before major skeletal development) it was assumed that the initial concentration in the embryo/fetus was the same as in the maternal “remaining tissue” so that a steady-state applied. In this situation, the usual decrease in concentration with growth does not apply.

At six and eight months there is again a steady-state situation for soft tissue radioactivity in the embryo/fetus that leads to concentrations about the same as in maternal “remaining tissue.” The literature suggests more complex kinetics, but the simplified dosimetric approximation assumed that the fetal bone concentration was maintained at concentrations that were twice those in fetal soft tissue, and the average total concentration is about 2.8 times that in maternal soft tissue.

The above remarks do not apply to insoluble forms of phosphorus such as chromic phosphate, which is used therapeutically by intraperitoneal or intrathoracic injection. With this, there is no or minimal blood uptake, with correspondingly no or little relevance to embryo/fetal dosimetry.

Based on the foregoing model, Sikov and Hui (1996) estimated dose rates and cumulated radiation doses to the embryo/fetus from intravenous injection of ^{32}P as sodium phosphate in pregnant women at various months of gestation. Initial dose rates following injection of 37 kBq at times after three months of gestation were roughly 1 mGy d^{-1} . Estimated cumulated doses between injection and term were 1.6 to 2.2 mGy MBq $^{-1}$ for all stages.

A.16 Sulfur

Sulfur (S, Z = 16) has four stable isotopes, ^{32}S to ^{34}S and ^{36}S . It has seven radioisotopes in the range of ^{29}S to ^{31}S and ^{35}S to ^{38}S , with half-lives from less than 1 s to 87.2 d (^{35}S).

A.16.1 Biological Information

Absorption of sulfur from the GI tract is considered to vary from 0.1 for elemental sulfur through 0.8 for inorganic compounds to essentially 1.0 for organic sulfur as present in foods (ICRP, 1993). At early times after injection inorganic sulfur is fairly uniformly distributed throughout the various organs and tissues of the body.

About 80 percent of the administered activity is excreted. The retained components have biological half-lives of 20 and 2,000 d. Sulfur in organic compounds such as cysteine and methionine may be retained tenaciously (ICRP, 1993).

A.16.2 Fetal/Placental Information

Dziewiatkowski (1953) studied sulfate metabolism in the rat fetus, using ^{35}S . In humeri of fetuses at 20 dg, the concentration of ^{35}S was 30 times that in the maternal sternum. In the same fetuses the concentration of the isotope was also higher in the skeletal muscle, brain, heart and skin than in the corresponding maternal tissues, but that in the GI tract and contents was lower. Placental transfer has also been demonstrated in larger animal species, with major differences between cows, sheep and pigs, as well as in the fetal to maternal concentration ratio (Hansard, 1969).

Sulfur containing organic molecules such as methionine are actively transported to the fetus (Ishiwata *et al.*, 1985). The concentrations in fetal blood are initially about twice those in the woman's blood but fall within an hour, presumably due to deposition in fetal tissue (Gaull *et al.*, 1973). These workers also found metabolically related differences among the behavior of sulfur containing amino acids.

A.17 Chlorine

Chlorine (Cl, Z = 17) has two stable isotopes, ^{35}Cl and ^{37}Cl , and nine radioisotopes, ^{31}Cl to ^{34}Cl , ^{36}Cl and ^{38}Cl to ^{41}Cl . It is a normal component of all organs and tissues of the body.

Chlorine-36 crosses the placenta, but not as readily as tritium does. Only half as much ^{36}Cl as tritium was found in fetal rat lipids 24 h after administration, and the level of ^{36}Cl declined more rapidly. However, it has been noted that increasing amounts of ^{36}Cl cross the placenta as gestation advances (Cunningham and Lawrence, 1977).

Dancis *et al.* (1981) studied the transfer of ^{36}Cl and other substances across the perfused human placenta. It was found that the clearance index (clearance of test substance/clearance of antipyrine) for chloride (0.36 to 0.46) was slightly higher than for sodium (0.28) or urea (0.34 to 0.47).

A.18 Argon

Argon (Ar, Z = 18) has three stable isotopes, ^{36}Ar , ^{38}Ar and ^{40}Ar , and twelve radioisotopes, ^{32}Ar to ^{35}Ar , ^{37}Ar , ^{39}Ar and ^{41}Ar to ^{46}Ar . Argon is a stable gas with no soluble compounds.

A.19 Potassium

Potassium (K, Z = 19) has two stable isotopes, ^{39}K and ^{41}K , and fifteen radioisotopes, ^{35}K to ^{38}K , ^{40}K and ^{42}K to ^{51}K . The radioisotope ^{40}K emits beta rays and has a half-life of 1.28×10^9 y and a natural abundance of 0.0117 percent of potassium. It is a major contributor to the natural background radiation, both as an external and as an internally distributed source.

The body content of potassium in Reference Man is 140 g of which 120 g is in soft tissue and daily intake is 3.3 g (ICRP, 1975). Tissue concentrations of potassium are controlled by homeostasis and are essentially independent of intake rates or amounts under ordinary circumstance. As a consequence, radiation dose rates from natural ^{40}K in potassium are likewise independent.

There is an extensive literature presenting and analyzing measurements of the content, concentration and ratios of potassium in the fetus and fetal tissues at sequential times through gestation of humans and animals. Less information is available concerning kinetics.

In studies in two pregnant women at term, Neslen *et al.* (1954) calculated that the rate of potassium exchange between amniotic fluid and the maternal system was 0.0041 mole h⁻¹. Much of the kinetic information about the physiological behavior of potassium, including its placental transfer and disposition in the embryo/fetus, has been obtained from studies with the ^{86}Rb radioisotope of its analog rubidium.

A.20 Calcium

Calcium (Ca, Z = 20) has six stable isotopes, ^{40}Ca , ^{42}Ca , ^{43}Ca , ^{44}Ca , ^{46}Ca and ^{48}Ca , and 10 radioisotopes, ^{36}Ca to ^{39}Ca , ^{41}Ca , ^{45}Ca , ^{47}Ca and ^{49}Ca to ^{51}Ca . The most commonly used radioisotope, ^{45}Ca (β^- , gamma, half-life 163.8 d), is used for metabolic studies.

A.20.1 Biological Information

Calcium is a normal constituent of all body cells and fluids. Most of the calcium in the bodies of mammals is in the mineral bone with a reference value of about 1 kg and an assumed daily intake of 1.1 g (ICRP, 1975). Calcium is important in the blood clotting mechanism.

GI uptake in the normal adult is influenced by vitamin D and other factors but is usually considered to be in the range of 0.3. Absorption is considered to be increased to 45 percent by mid-pregnancy and recommended dietary levels are increased for pregnant and lactating women.

A.20.2 Fetal/Placental Information

Numerous studies have examined the progressively increased levels of calcium in the fetus and fetal skeleton and the several metabolic and structural correlates (Griessel, 1987; Widdowson, 1968). The use of radiocalcium for studies of pregnant mice was introduced in 1941 (Pecher and Pecher, 1941). Placental transfer of calcium has been studied in a variety of mammalian species, including cows, guinea pigs, monkeys, opossums, rats, sheep and swine (Comar *et al.*, 1955; Pecher and Pecher, 1941; Plumlee *et al.*, 1952; Ramberg *et al.*, 1973; Shirley *et al.*, 1954; Twardock, 1967; Twardock *et al.*, 1969; Wasserman *et al.*, 1957).

Calcium-45 has been used in studies of the uptake and binding by membrane fractions of the placenta in humans (Whitsett and Tsang, 1980). In monkeys the bi-directional transport of ^{45}Ca and ^{49}Ca was found to have a rate 6 to 10 times that required for growth (MacDonald *et al.*, 1965a).

It has long been known that the transfer of calcium across the placenta is most rapid toward the end of the gestation period (Huggett, 1941). Normally, the calcium transferred to the fetus is derived from maternal dietary calcium (Bronner, 1960). In studies involving reduced calcium intake by the mother, however, a normal concentration of calcium in the blood was maintained by withdrawing calcium from maternal bones; fetal calcium content was equal to that in controls (Bawden and McIver, 1964; Bawden and Osborne, 1962a; 1962b).

The kinetics of ^{45}Ca distribution in cows during late pregnancy has been studied, using a four-compartment model (Ramberg *et al.*, 1970). Ramberg *et al.* (1973) developed an eight-compartment model of the maternal-placental-fetal calcium system in sheep.

They found a mean transfer rate from mother to fetus of $212 \text{ mg d}^{-1} \text{ kg}^{-1}$ fetal body weight, and a mean transfer rate from fetus to mother of $12 \text{ mg d}^{-1} \text{ kg}^{-1}$ fetal body weight. In data from monkeys analyzed with the same model, the calcium transfer from mother to fetus was $390 \text{ mg d}^{-1} \text{ kg}^{-1}$ and the return flow rate was $325 \text{ mg d}^{-1} \text{ kg}^{-1}$. The authors cite other studies that indicate that the daily calcium accumulation is 150 to 500 $\text{mg kg}^{-1} \text{ d}^{-1}$ in sheep fetuses, $200 \text{ mg kg}^{-1} \text{ d}^{-1}$ in bovine fetuses, and about $26 \text{ mg kg}^{-1} \text{ d}^{-1}$ in human fetuses.

In a double tracer experiment using rats and pigs, Comar (1956) showed that the placenta discriminates between strontium and calcium, the strontium/calcium ratio in the fetus being about half that in the mother. Rivera (1963) found a weaker discrimination (82 percent) in humans by comparing concentrations in the blood from the fetal and maternal sides of the placenta immediately after birth.

A.21 Scandium

Scandium (Sc, Z = 21) has one stable isotope, ^{45}Sc , and 11 radioisotopes, ^{40}Sc to ^{44}Sc and ^{46}Sc to ^{51}Sc .

It is assumed that the fractional uptake of scandium from the GI tract is 0.0001 (ICRP, 1981). Animal studies indicate that intravenously or intramuscularly injected scandium is preferentially deposited in liver, kidney, spleen, bone and to some extent lung. In humans, the whole-body retention has been studied for 584 d after the intravenous injection of ^{46}Sc nitrilotriacetate (Rosoff *et al.*, 1965).

For dosimetry it is assumed that of scandium leaving the blood, 40 percent, 30 percent, and 10 percent are translocated to the skeleton, liver and spleen, respectively. The remainder is assumed to be uniformly distributed in the rest of the body. Of the scandium deposited in any organ or tissue, 10 percent and 90 percent are assumed to be retained with biological half-lives of 5 and 1,500 d, respectively.

No studies involving pregnancy were found.

A.22 Titanium

Titanium (Ti, Z = 22) has five stable isotopes, ^{46}Ti to ^{50}Ti , and eight radioisotopes, ^{41}Ti to ^{45}Ti and ^{51}Ti to ^{53}Ti .

It is assumed that the fractional absorption into the blood from the GI tract or by inhalation is 0.01 for all compounds of titanium (ICRP, 1981). Stable titanium is fairly uniformly distributed throughout the body although occasional high levels are found in the lungs, probably due to the inhalation of titanium-containing dusts.

For dosimetry it is assumed that titanium leaving the blood is uniformly distributed throughout the body and that it is retained with a biological half-life of 600 d.

No studies involving pregnancy were found.

A.23 Vanadium

Vanadium (V, Z = 23) has one stable isotope, ^{51}V , and 10 radioisotopes, ^{44}V , ^{46}V to ^{50}V and ^{52}V to ^{55}V . Naturally occurring ^{50}V , half-life 3.9×10^{17} y, has an abundance of 0.250 percent of vanadium. The other radioisotopes have half-lives of less than 1 h, except ^{48}V (15.98 d) and ^{49}V (331 d).

A.23.1 Biological Information

It is assumed that the fractional absorption of dietary vanadium is 0.01 for all compounds of vanadium, although this may overestimate the GI absorption of some compounds (ICRP, 1981). Vanadium is regarded both as an essential trace element and as a toxic metal (Hackett and Kelman, 1983). In the blood, vanadium tends to bind with serum proteins, in contrast to other toxic metals (lead, cadmium, mercury) which bind to erythrocytes.

For dosimetry, it is assumed that, of vanadium leaving the transfer compartment, 70 percent goes directly to excretion, 25 percent is translocated to mineral bone, and 5 percent is uniformly distributed throughout the rest of the body (ICRP, 1981). Vanadium is assumed to be retained in any organ or tissue with a biological half-life of 10,000 d.

A.23.2 Fetal/Placental Information

Maternal exposures correlate poorly with subsequent fetal body burdens. Vanadium concentrates in the fetal membranes and placenta of the rat, and relatively small amounts reach the fetus (Hackett and Kelman, 1983). Following intravenous maternal administration of "high" doses of vanadium in rats at 9 or 19 dg,

there were no effects on the fetus, but increased embryo mortality and skeletal defects were observed with administration at 15 dg. The extent to which these effects are species-specific has not been established.

A.24 Chromium

Chromium (Cr, Z = 24) has four stable isotopes, ^{50}Cr , ^{52}Cr , ^{53}Cr and ^{54}Cr , and nine radioisotopes, ^{45}Cr to ^{49}Cr , ^{51}Cr and ^{55}Cr to ^{57}Cr . Most of the radioisotopes are short lived, but ^{51}Cr has a half-life of 27.7 d. This isotope is a gamma emitter that has been used to label blood cells for clinical evaluations.

A.24.1 Biological Information

The absorption of chromium from the GI tract into blood varies from less than 0.005 to 0.1 or more, depending upon the compound administered. For dosimetry purposes it is assumed that the absorption for chromium in the trivalent state is 0.01, and is 0.1 for chromium in the hexavalent state (ICRP, 1980). It is also assumed that chromium entering the GI tract following inhalation is in the hexavalent state.

The retention of chromium in the body also depends on the chemical form and route administered. In particular, sodium chromate has a marked affinity for erythrocytes, and ^{51}Cr is used to label erythrocytes. Chromic chloride does not penetrate the erythrocyte membrane (Korst, 1968). Chromium in erythrocytes disappears from the circulation of normal persons with a biological half-life of approximately 30 d. Normal subjects excrete about 25 percent of chromium that is intravenously injected in the chromic form in the first 24 h post-injection period. It is assumed that 0.05 of absorbed chromium goes to bone, where it is retained with a biological half-life of 1,000 d.

A.24.2 Fetal/Placental Information

As indicated for the adult, chromium transfer into the embryo also depends on chemical form and route of entry (Mertz *et al.*, 1969). The placental transfer of trivalent ^{51}Cr as potassium chromate (EC, gamma, half-life 27.704 d) has been studied in rats; results showed substantial uterine and fetoplacental deposition at 3 d after intravenous administration (Wallach and Verch, 1984). In

studies with the rhesus monkey, Wallenburg *et al.* (1978) found that ^{51}Cr ions crossed the placenta, but ^{51}Cr -labeled platelets did not. Extrapolating the monkey data to a human fetus with a weight of 1,700 g (about 31 weeks of pregnancy), they estimated that an administered 0.74 MBq of ^{51}Cr -labeled platelets would give a total radiation dose of 74 μGy to the fetus. For ^{51}Cr -labeled erythrocytes, the RIDIC/ORISE (Watson, 1992a) biological model for the adult is based on the ICRP Publication 53 (ICRP, 1987) model with modifications that use blood to determine total body residence time, and then subtract liver, spleen and red marrow residence times to obtain cumulated activities for the remainder of the body.

Reported values vary, but in conservative estimates 29 percent of the activity from intravenously injected labeled red cells is retained in "other tissues" and is considered to be available for transfer across the placenta. Cumulated radiation doses to the non-pregnant uterus, a surrogate for dose to embryo/fetus is estimated as 0.1 $\mu\text{Gy kBq}^{-1}$, and the corresponding dose to a three month fetus as 0.08 $\mu\text{Gy kBq}^{-1}$ following intravenous injection of ^{51}Cr -labeled erythrocytes (Stabin, 1992).

Chromium chloride is present as a contaminant with labeled erythrocytes and therefore is considered in dose calculations. Such calculations indicate an impact on the dose to the fetus of less than 10 percent of that from the labeled erythrocytes.

A.25 Manganese

Manganese (Mn, Z = 25) has one stable isotope, ^{55}Mn , and 12 radioisotopes, ^{49}Mn to ^{54}Mn , ^{56}Mn to ^{60}Mn and ^{62}Mn .

A.25.1 Biological Information

Inorganic compounds of manganese are poorly absorbed from the GI tract. For dosimetry, a fractional absorption value of 0.1 is assumed for all compounds of manganese (ICRP, 1979).

The metabolism of manganese is influenced by the levels of manganese and iron in the blood (Britton and Cotzias, 1966; Mahoney and Small, 1968). Human studies by Mahoney and Small (1968) have shown that 30 percent of the whole-body retention of manganese in the first 60 d has a 4 d halftime and 70 percent has a 33 d halftime.

Based on animal studies it is assumed that of manganese entering the transfer compartment, 35 percent goes to bone and is

retained there with a half-life of 40 d. Of the remainder, 25 percent is assumed to go to the liver and be retained there with half-lives of 4 d (10 percent) and 40 d (15 percent) and 40 percent becomes uniformly distributed in the rest of the body; equal amounts are retained with half-lives of 4 d and 40 d, respectively. All isotopes of manganese are assumed to be uniformly distributed over bone surfaces at all times following their deposition in the skeleton.

A.25.2 Fetal/Placental Information

Manganese is found in fetal bone and liver, but no stores are believed to exist and the hepatic concentration appears to be constant through gestation (Lönnnerdal, 1988). No information was found concerning administration during pregnancy.

A.26 Iron

Four stable isotopes of iron (Fe, Z = 26) are found in nature, ^{54}Fe , ^{56}Fe , ^{57}Fe and ^{58}Fe but ^{56}Fe (91.7 percent) is predominant. Radioactive isotopes from ^{52}Fe to ^{61}Fe are listed in tables of isotopes, but many have half-lives of less than 1 h. The radioisotopes of radiological importance include ^{52}Fe (half-life of 8.3 h) which decays by positron emission and by electron capture to radioactive ^{52m}Mn (half-life = 21.1 min) which then decays to ^{52}Mn (half-life = 5.6 d). Decay of ^{55}Fe (half-life = 2.7 y) is by electron capture to stable ^{55}Mn . The decay mode of ^{59}Fe (half-life = 44.5 d) is by beta emission to stable ^{59}Co .

A.26.1 Biological Information

Iron is a natural constituent of the human body and the iron content of Reference Man is 4.2 g with soft tissues containing 3.3 g (ICRP, 1975). In men, about 70 percent of the iron is in hemoglobin, 27 percent in storage as ferritin and hemosiderin, and about 6 percent in other compartments (ICRP, 1987; Robertson *et al.*, 1983). The ICRP (1995) assigned 0.1 as the fractional absorption of all compounds of iron from the GI tract in the normal adult.

Women have less storage and total body iron than men and absorb up to four times more iron. Ferrous salts may be absorbed to a greater extent than ferric salts. Because the fetus depletes maternal stores of iron, absorption of iron by the pregnant woman

rises from 11 percent at 10 weeks to 41 percent during the last month (Bothwell and Finch, 1962).

Discussions and models of metabolism of iron for dosimetric purposes are available in ICRP publications (ICRP, 1980; 1987; 1995). In a model developed for the normal individual (Robertson *et al.*, 1983), iron is assumed to accumulate in red marrow after it is cleared from plasma. There the iron is incorporated into red blood cells where it remains until the death of the cell. The iron is then released and the utilization cycle is repeated. For radioisotopes with short half-lives, the activity may decay before the iron becomes incorporated into red blood cells. The model assumes that no activity is excreted from the body.

A.26.2 Fetal/Placental Information

Extensive animal experiments have studied the kinetics of iron compounds in pregnancy. Seal *et al.* (1972) compared placental transfer of ^{59}Fe in 16 species and found two major routes of iron transfer to the mammalian fetus. In species with hemochorial placentation, by 2 to 3 h five percent or more of maternally injected ^{59}Fe had been transferred to the near-term fetus. In these species, the rapid route involves the release from transferrin of serum iron to the placenta and its movement into the fetal circulation. In species that do not have hemochorial placentation, the route appears to be through release of maternal hemoglobin from extravasated red cells. This would seem to indicate that animals such as dogs, cats, sheep and pigs are not representative of iron transfer in humans.

The large amounts of iron transferred to the fetus are not carried across the placenta by transferrin. Rather, the iron is transferred to mediators that carry the iron into the fetus, probably receptors on trophoblasts. Okuyama *et al.* (1985) have suggested that in animals with hemochorial placentas iron transport from mother to fetus may be one-way. According to Glasser *et al.* (1969), as well as other investigators, the maturing fetus makes greater demands on available iron, and the ability of the placenta to clear iron from the maternal plasma and transfer it to the fetus is enhanced at later stages of gestation. The mechanisms by which iron traverses the human placenta are not clear, but near-term transfer is achieved against a concentration gradient (Fletcher and Suter, 1969). Transfer is maintained in the presence of inadequate maternal iron stores, thus causing or aggravating iron deficiency in the mother (Beaton, 1981). These data suggest that placental

transfer of iron involves an active transport mechanism (Galbraith *et al.*, 1980).

van Dijk (1977) developed a compartmental model of iron transport from results of experiments on nine pregnant rhesus monkeys. In some animals ^{59}Fe was injected into the maternal circulation and the transport into the fetus was determined. In others the iron was injected into the fetal circulation. Results show that transport from mother to fetus is probably much more efficient than transport in the reverse direction. Transfer rate constants calculated for a five-compartmental system agree well with the compartmental model of Robertson *et al.* (1983).

Studies in women measured iron content in placentas, maternal blood, and fetal blood (Baglan *et al.*, 1974). These measurements showed that maternal and fetal blood concentrations are approximately equal while concentration in the placenta is three to four times lower. After oral administration of ^{59}Fe to 819 women early in their pregnancy, Hahn *et al.* (1951) found one to three percent of the administered activity was in fetal blood at birth.

Dyer and Brill (1969) and Dyer *et al.* (1973) extended these studies by evaluations of patients who were to receive therapeutic abortions and through studies in sheep. Concentrations in fetal liver were about 200 times higher than in the remainder of human fetuses through midgestation but sheep displayed a lesser differential. Based on a consolidation of their overall data, they estimated a dose factor of $10.3 \text{ mGy kBq}^{-1}$ to the total fetus with administration in the period of 9 through 22 weeks of gestation, with a roughly ten-fold higher fetal liver dose.

A.26.3 Radiation Dose Estimates

Dyer *et al.* (1973) made further estimates of absorbed radiation doses to the fetuses of three pregnant women from the series of Hahn *et al.* (1951) because the children later developed malignancies. One fetus exposed at 13 weeks was estimated to receive 1 mGy from 94.7 kBq ; one exposed at 23 weeks was estimated to receive 18 mGy from $1,643 \text{ kBq}$; and one exposed at 20 weeks was estimated to receive 0.36 mGy from 33.3 kBq . Stabin *et al.* (1997) have recalculated these values using the more recent MIRDOSE 3 program.

Roedler (1987) used reported values to calculate activity concentrations of iron in the adult and the fetus from weeks 9 to 22 of gestation. The ratio of activity concentration in the fetal liver to that in the adult was given as 80. The effective halftimes for ^{59}Fe ,

corrected for growth, were estimated to be 45 d ($T_{eff} = T_{phys}$) in the adult and 3.2 d in the fetus. In the fetus, a fraction of 0.12 was assumed to be in storage with $T_{eff} = 10.7$ d and 0.88 in erythropoiesis with $T_{eff} = 2.2$ d. Roedler estimated the liver doses in the fetus as 28 mGy MBq⁻¹ and in the adult as 12 mGy MBq⁻¹.

As described in Section 7, the radiation dose to the fetus can be estimated from residence times calculated by the compartmental analysis technique. An illustration of this approach is provided by the calculated dose estimates to the fetus from an intake of radioiron by the mother as presented in Tables A.1 and A.2. The studies of iron metabolism and placental transfer in pregnant rhesus monkeys by van Dijk (1977), and the resulting five-compartment model and model of iron metabolism described by Robertson *et al.* (1983), were employed. Two of van Dijk's experiments (3 and 4) were chosen as representative of the results and used to calculate residence times for iron in the pregnant woman. The residence times for ⁵²Fe, ⁵⁵Fe and ⁵⁹Fe in maternal tissues calculated from the data of van Dijk are compared with those from MIRD Dose Estimate Report No. 11 (Robertson *et al.*, 1983) in Table A.1. This Table also lists the residence times of iron radioisotopes in the placenta and fetal tissues as derived from the transfer rate constants developed by van Dijk (1977) for Experiments 3 and 4.

The absorbed dose estimates for the fetus through the first five months of pregnancy (Table A.2) were calculated using S values from a mathematical model describing the nongravid uterus for early pregnancy (C[h]risty and Eckerman, 1987) and from a mathematical model describing the uterus and fetus for the period from three through five months (Davis *et al.*, 1987). These give values

Table A.1—Residence times (hours) of iron in maternal, placental and fetal tissues and comparison with MIRD estimated value.

Source Organ	⁵² Fe		⁵⁵ Fe		⁵⁹ Fe	
	Exper. 3	Exper. 4	Exper. 3	Exper. 4	Exper. 3	Exper. 4
Maternal tissues	11.3	11.7	32,070	33,500	1,430	1,500
Placenta	0.0093	0.0047	0.012	0.0058	0.012	0.0058
Fetal plasma	0.20	0.081	0.37	0.15	0.37	0.15
Fetal tissues	0.47	0.19	2,400	960	110	43
MIRD Dose Estimate No. 11	(11.8)		(32,600)		(1,450)	

Table A.2—*Absorbed dose estimates for the fetus from intake of radioiron by the mother^a (mGy MBq⁻¹).*

Radioisotope	0 through 2 Months Pregnancy		3 through 5 Months Pregnancy	
	Exper. 3	Exper. 4	Exper. 3	Exper. 4
⁵² Fe	1.2	0.50	0.26	0.088
⁵⁵ Fe	100	41	18	7.1
⁵⁹ Fe	150	63	34	15

^aEstimates based on Experiments 3 and 4 of van Dijk (1977), that involved injection of iron bound to rhesus monkey transferring into the maternal circulation, and using the iron kinetic model of Robertson *et al.* (1983).

that are somewhat higher than those estimated for ⁵⁹Fe by Dyer and Brill (1969) or by Sikov and Hui (1996) but are lower than inferred from the estimate of Roedler (1987) for the liver.

A.27 Cobalt

The only stable isotope of cobalt (Co, Z = 27) is ⁵⁹Co, but there are numerous radioisotopes in the range of ⁵⁴Co to ⁶⁴Co; many of these have half-lives less than 1 h. Of those with longer lives, ⁵⁵Co has a half-life of 17.5 h and decays by positron emission and electron capture; ⁵⁶Co has a half-life of 78.8 d and decays of electron capture and positron emission; ⁵⁷Co has a half-life of 271.8 d and decays by electron capture; ⁵⁸Co has a half-life of 70.9 d and decays by electron and positron emission; ^{58m}Co has a half-life of 9.2 h and decays by isomeric transition; and ⁶⁰Co has a half-life of 5.27 y and decays by beta emission.

A.27.1 Biological Information

Cobalt is a natural constituent of the human body and the cobalt content of Reference Man is 1.5 mg with 0.11 mg in the liver (ICRP, 1975). Absorption of cobalt oxide from the GI tract is minimal, but absorption of dietary cobalt is somewhat greater. In ICRP Publication 67 (ICRP, 1993), the ICRP chose 0.1 as the absorption fraction from the GI tract for organically complexed compounds of cobalt and for unspecified compounds. For inorganic compounds ingested in tracer quantities and for oxides and hydroxides, an f_1 value of 0.1 was adopted (ICRP, 1993). This ICRP publication discusses the distribution and retention of cobalt.

For use in medicine, vitamin B₁₂ has been labeled with cobalt isotopes, usually ⁵⁷Co and ⁵⁸Co, to determine vitamin B₁₂ kinetics and turnover of the vitamin in patients with pernicious anemia. Biokinetic models (ICRP, 1987) have been developed for four different methods of administering cobalt-labeled vitamin B₁₂: (1) intravenous injection with no carrier vitamin B₁₂, (2) glomerular filtration rate studies by intravenous injection with carrier vitamin B₁₂, (3) oral administration without flushing with stable vitamin B₁₂, and (4) oral administration with a flushing amount of unlabeled vitamin B₁₂.

A.27.2 Fetal/Placental Information

Evaluations of cobalt-labeled vitamin B₁₂ in animals include those of Mahon *et al.* (1973) who studied the distribution of ⁵⁷Co-vitamin B₁₂ in pregnant rabbits. At 1 h after administration, the concentration of cobalt in the placenta was 0.35 of that in the maternal blood and 110 times that in the fetal blood. The blood contained 89.6 percent of the administered activity at 1 h, the liver 5.6 percent, kidneys 1.8 percent, marrow 9.5 percent, placenta 0.26 percent, and fetus 0.01 percent.

Ullberg *et al.* (1967) measured fetal accumulation of labeled vitamin B₁₂ in pregnant mice. After 15 min the concentration in the maternal blood was lower than in most tissues and after 4 h it was almost nondetectable. The uptake in the placentas was the highest of all tissues, reaching peak concentration at about 1 h after administration with a slow transportation of radioactivity from the placentas to the fetuses. The transfer through the placenta showed similarity to the absorption of vitamin B₁₂ in the intestine of rats, indicating the transport mechanism for the placenta may be similar to that for the intestine.

The fetal concentration had reached its maximum by 24 h (Ullberg *et al.*, 1967). The fetal tissues had much higher concentrations than the maternal tissues, but the fetal uptake was dependent upon the amount of vitamin B₁₂ administered. With small amounts (0.02 µg), the fetuses showed 130 times higher concentrations than the maternal tissues, and the retention of the cobalt-labeled vitamin B₁₂ was prolonged (95 percent after 24 h). With larger amounts (2.5 µg), the fetuses showed 5.5 times higher concentrations than the maternal tissues, and only 11.3 percent was retained after 24 h. When 0.05 µg of vitamin B₁₂ was administered, a mean of 90 percent of the administered activity was found in pregnant mice at 24 h after injection and a mean of 83.3 percent

in nonpregnant animals. From 15 min to 2 h, more than one-half of the injected activity was in the placentas. The activity in the fetuses was more than seven times higher than in the maternal tissues which contained only about 10 percent of the mean activity. In the fetuses the cobalt was not located in a storage organ but was distributed to all fetal tissues. In the mother and the fetuses the highest concentrations were found in the endocrine organs, renal cortex, and gastric mucosa. In animals killed 16 to 32 d after injection, some redistribution had occurred and the fetal concentration was somewhat lower, probably as a result of fetal growth.

Cobalt chloride also has been examined in experimental animals. Placental transfer of ^{60}Co chloride was measured as a function of gestational age in rats (Zylicz *et al.*, 1976). The concentration of ^{60}Co in fetal blood after injection on 20 dg was about four times greater than that in maternal blood. The activity concentrations in fetal liver and kidney were much lower than those in maternal liver and kidney. The concentration in the fetal liver tissue was about 1.5 times that in fetal kidney. The retention of ^{60}Co in the whole maternal body was not significantly different from that in control nonpregnant rats; however, the radioactivity in the fetoplacental unit increased markedly over time (Zylicz *et al.*, 1976). The concentrations in maternal liver and kidney during the last days of gestation were less than those in nonpregnant rats, probably as the result of an increasing demand for cobalt by the rapidly growing fetuses.

Autoradiographic studies on distribution of radiocobalt chloride in pregnant mice (Flodh, 1968) showed the highest concentration of $^{60}\text{CoCl}$ in the dams to be in the cartilaginous structures, liver, kidneys and pancreas. The total fetal accumulation of ^{60}Co at all intervals studied was lower than that of the mother. A selective accumulation, as high as in the maternal cartilages, was seen in the fetal skeleton during the first days after administration. The uptake was highest in hyaline cartilage of the type that remains as cartilage in the adult animal. The fetal cranial bones, like the cranium of the dam, also showed high accumulations of cobalt. These are the only bones in the body which are formed through intramembranous ossification. Low concentrations were observed in soft tissues of the fetuses except liver, which showed a fairly high concentration 4 d after injection. After 16 d the fetuses had no noticeable radioactivity. The placenta showed a moderate accumulation of radiocobalt throughout the study, with a slight increase during the first 24 h after administration. The distribution pattern of radiocobalt was entirely different from that obtained by Ullberg

et al. (1967) which supports the view that vitamin B₁₂ is not metabolized to inorganic cobalt in the body.

The cobalt content of human placentas, maternal blood, and fetal blood was measured by Baglan *et al.* (1974). They found that concentrations in the maternal and fetal blood were approximately equal but the concentration in the placenta was about 10 times higher; however, all concentrations were low.

Tracer amounts of ⁵⁸Co vitamin B₁₂ were administered to pregnant dogs (Luhby *et al.*, 1959) and women (Luhby *et al.*, 1958) to determine the range and kinetics of placental transfer. Results showed that the transfer of single physiological administrations of ⁵⁸Co vitamin B₁₂ to the human fetus *via* the placenta varied from 0.3 percent to 28 percent of the amount administered to the mother. Substantial amounts were not transferred until 24 h after administration, but maximum transfer occurred within 15 to 21 d. The range of deposition of ⁵⁸Co vitamin B₁₂ after maximum placental transfer occurred was 1.5 to 2 percent. More than 90 percent of the ⁵⁸Co vitamin B₁₂ transferred was present in placental tissue rather than in placental blood.

A.27.3 Radiation Dose Estimates

Roedler (1987) calculated concentration ratios for cobalt in fetal and maternal tissues but gave no dose estimates. The concentration ratios (C_F/C_M) are 0.12 to 1.9 for cobalt chloride and 0.1 to 7.5 for cobalt vitamin B₁₂ for total body. The corresponding ratios for liver are 0.71 for cobalt chloride and 0.13 to 19.5 for cobalt vitamin B₁₂.

The calculated initial dose rates to the embryo/fetus from radio-cobalt chloride decrease slightly as it is administered to a pregnant woman at progressively later times of gestation. The corresponding cumulated radiation absorbed doses through the remainder of gestation, however, decrease by a factor of five (Sikov and Hui, 1996). Rough general values of cumulated doses for injection of 37 kBq of activity into the mother's blood at any of the several fetal stages of gestation are 0.5 mGy for ⁵⁷Co, 3 mGy for ⁵⁸Co, and 10 mGy for ⁶⁰Co. The corresponding overall stage-related values for oral administration of vitamin B₁₂ to a normal woman are five-fold greater than for ionic forms (Russell *et al.*, 1997b).

A.28 Nickel

The stable isotopes of nickel (Ni, Z = 28) are ^{58}Ni , ^{60}Ni , ^{61}Ni , ^{62}Ni and ^{64}Ni . The abundances of ^{58}Ni (67.8 percent) and ^{60}Ni (26.2 percent) predominate. Radioisotopes ranging from ^{56}Ni to ^{67}Ni have been listed in tables of isotopes, but many of these have half-lives less than 1 h. ^{59}Ni has a half-life of 8×10^4 y. Other radioisotopes with half-lives greater than 1 d are ^{56}Ni , ^{57}Ni , ^{63}Ni and ^{66}Ni .

A.28.1 Biological Information

Nickel is a natural constituent in the human body and the nickel content of Reference Man is 10 mg with 5.3 mg in soft tissue and less than 5 mg in skeleton (ICRP, 1975). The ICRP (1993) assigned 0.05 as the fractional absorption from the GI tract for radiological protection purposes. A review of the literature, discussion of metabolism, and a biokinetic model for nickel are given in these publications.

A.28.2 Fetal/Placental Information

Experiments in mice by Jacobsen *et al.* (1978) were performed to study passage of nickel through the placenta. They found higher concentrations in several fetal organs than in the maternal organs after intraperitoneal injection of nickel chloride into the mother. Concentrations of nickel in blood and placentas were found by Lu *et al.* (1976) to be at the maximum level (19.8 and 0.4 $\mu\text{g g}^{-1}$) 2 h after injection, while those of liver, spleen and kidney reached their maximum (4.9, 13.2 and 56.2 $\mu\text{g g}^{-1}$, respectively) 4 h after injection. The maximum concentration in fetal tissues (1.1 $\mu\text{g g}^{-1}$) was attained 8 h after injection. Only a slight gradual decrease in concentration was detected for 24 h thereafter.

The distribution and kinetics of injected nickel were studied by Mas *et al.* (1986) from intraperitoneal injections of $^{63}\text{NiCl}_2$ in control and pregnant rats on days 12 and 19 after impregnation. Preparations were studied using carrier-free ^{63}Ni and with added stable nickel (40 mg kg^{-1} body weight). The time-course of disappearance of radioactivity from the tissues and blood of the rat was determined, as well as the degree of incorporation of radioactivity. The mean biological halftimes were about 3 to 5 h without regard to the amount of stable nickel administered. Pregnancy had little effect

on the overall disposal of nickel though some changes were seen in individual organs.

Forty human fetuses of 22 to 43 weeks gestation were analyzed by Casey and Robinson (1978) for concentrations of several essential trace elements including nickel. Concentrations of nickel in fetal tissues were of the same order of magnitude as those reported for most maternal tissues. Adult kidney and bone levels were higher than the fetal range. Casey and Robinson determined that nickel crosses the placenta readily, and the supply to the fetus would depend on the status of nickel in the mother.

Roedler (1987) used available data including that of Jacobsen *et al.* (1978) to determine concentration ratios for nickel in maternal and fetal tissues. Ratios range from 0.092 in total body, to 3.5 in liver, 4.1 to 19.5 in bone, and 24.5 in brain. No estimates of dose were presented.

A.29 Copper

The stable isotopes of copper (Cu, Z = 29) and their abundances are ^{63}Cu (69.1 percent) and ^{65}Cu (30.9 percent). Radioisotopes ranging from ^{57}Cu to ^{68}Cu are listed in tables of isotopes, but many of these have half-lives less than 1 h and only ^{67}Cu has a half-life greater than 1 d.

A.29.1 Biological Information

Copper is a natural constituent in the human body that plays a significant role in developing and maintaining myelin. It is also an integral part of several critical enzymes and cofactors (Henkin *et al.*, 1971). The copper content of ICRP Reference Man (ICRP, 1975) is 72 mg with 65 mg in soft tissue. The fractional uptake of copper from the GI tract in the human is in the range 0.32 to 0.9.

For radiological protection purposes, 0.5 was assigned as the fractional absorption from the GI tract for all compounds of copper (ICRP, 1980). That ICRP report adopted and described a metabolic model for copper that conformed to Reference Man (ICRP, 1975).

A.29.2 Fetal/Placental Information

The human fetus markedly accumulates copper during the third trimester so that the whole body contains about 18 mg, half of which is in the liver. This proportion is significantly higher than in

adults and is bound to proteins, especially metallothioneine (Lönnertdal, 1988).

Casey and Robinson (1978) determined concentrations of several essential trace elements in 40 human fetuses of 22 to 43 weeks of gestation. Copper concentrations in the liver were as much as 100 times those in other tissues, but only concentrations in the brain showed significant increase with gestational age, increasing from a mean of $6.27 \mu\text{g g}^{-1}$ dry matter at 22 to 25 weeks to $12.2 \mu\text{g g}^{-1}$ at term. This may be associated with the requirement for copper in phospholipid synthesis, particularly in the myelin sheaths. The liver concentrations of 91 to $566 \mu\text{g g}^{-1}$ (mean of $276 \mu\text{g g}^{-1}$) were much higher than levels found in New Zealand adults. The ICRP (1975) gives a mean of 0.012 g in the 1,800 g liver of Reference Man for a concentration of $6.7 \mu\text{g g}^{-1}$.

Henkin *et al.* (1971) studied copper and zinc concentrations in venous blood from 15 normal mothers and from the umbilical cords of their 15 normal babies. Amniotic fluid was obtained from four of the mothers. They found that fetal serum binding of copper is not significantly different from that of normal adults, suggesting that copper moves across the placenta by passive transfer.

A.30 Zinc

The stable isotopes of zinc (Zn , $Z = 30$) are ^{64}Zn , ^{66}Zn , ^{67}Zn , ^{68}Zn and ^{70}Zn . The most abundant are ^{64}Zn (48.9 percent), ^{66}Zn (27.8 percent), and ^{68}Zn (18.6 percent). Radioisotopes ranging from ^{60}Zn to ^{72}Zn are listed in tables of isotopes, but many of these have half-lives less than 1 h. Only ^{65}Zn , which is a common environmental contaminant, and ^{72}Zn have half-lives greater than 1 d.

A.30.1 Biological Information

Zinc, a natural constituent of the human body, is important for protein synthesis and is essential for growth, sexual maturation, and wound healing (Chabe *et al.*, 1973). The zinc content of ICRP Reference Man (ICRP, 1975) is 2.3 g with 1.8 g in soft tissues. The fractional uptake of orally administered zinc from the GI tract has been reported to be between 0.31 and 0.51 (ICRP, 1980). The daily intake of the element may affect this value and fractional uptakes of as much as 0.9 may occur (Furchner and Richmond, 1962; Richmond *et al.*, 1962). The ICRP discussed the metabolism of zinc

and assigned 0.5 as the fractional absorption of all compounds of zinc from the GI tract (ICRP, 1980; 1993).

Richmond *et al.* (1962) studied the retention of orally administered zinc in mice, rats, dogs and humans. Their data, showing that zinc is more tenaciously retained in the skeleton than in other tissues, agree with the distribution of stable zinc given for Reference Man (ICRP, 1975).

A.30.2 *Fetal/Placental Information*

Zinc has a profound effect on embryonic and fetal development (Ferm and Hanlon, 1974). The transfer of zinc across the placenta has been studied in several species and it is clear that diets deficient in zinc can lead to congenital malformations (Takacs *et al.*, 1984). Zyllicz *et al.* (1975a) examined the placental transfer in rats and also compared zinc retention in nonpregnant and pregnant animals. They found that ^{65}Zn retention in pregnant rats is decreased as compared with nonpregnant rats.

Terry *et al.* (1960) injected pregnant rabbits with ^{65}Zn at 21 dg; the placenta contained the greatest part of the zinc recovered in the products of conception during the first 2 h after injection but the fetal activity approached the placental activity by 200 min. When administration was made on the 29th dg, the placenta apparently lost the radioactive zinc more rapidly than the fetus. The fetal and placental content were equal at about 1.2 h after administration; after that time the fetal activity continued to increase and the placental activity to decrease. The maximum recovery of ^{65}Zn in the fetoplacental unit was approximately eight percent and occurred at 24 h after injection (Terry *et al.*, 1960).

A sharp upsurge of radiozinc uptake occurred between the 20 and 22 dg. This is similar to findings with radioiron and may suggest a critical period in metal transport across the placenta. The speed of zinc transport across the placenta was slower than the rapid transport of radioiron. The transfer of radiozinc does become more rapid at later stages of pregnancy, indicating a more efficient mechanism of placental transport with advancing pregnancy (Matsusaka, 1978; Terry *et al.*, 1960). The results of Schulert *et al.* (1969) showed that the most rapid uptake of zinc occurred at day 17 when the uptake was about twice that observed on either day 14 or day 20. On days 14 and 17 the relative uptake of zinc was more than twice that of calcium but at day 20 was only a little more than half that of calcium, suggesting that by day 20 the demands of the developing fetus for zinc have largely been met.

In studies with mice injected on day 12, 15, 17 and 18 of gestation, Matsusaka (1977) found that, except for animals injected on day 18, the fetal contribution increased with the progression of gestation. Each of the pups was born with three to four percent of the overall maternal body burden so that the litter accounted for 40 to 45 percent of the total maternal body burden prior to their birth. In the day 18 group, the fetal contribution was somewhat smaller than that of the other groups.

Hansard (1969) studied the distribution of ^{65}Zn in gilts, ewes and heifers during the third trimester of pregnancy. In the gilts, the placenta contained about 47 percent of the activity recovered in the products of conception and the fetuses contained about 53 percent. In the ewes and heifers, the placenta contained about 41 percent and the fetuses about 59 percent. The percent of injected activity in the maternal liver decreased from 18.4 at 12 h after injection to 9.8 at 168 h, but the activity in the liver of the fetuses (calculated as total in litter of eight pigs) increased from 0.05 percent at 12 h to 1.44 percent at 168 h. The activity in the heart, kidney and spleen remained approximately the same over this time period.

Ferm and Hanlon (1974) found that the hamster placenta is permeable to zinc during the early critical stage of embryogenesis (days eight to nine). This is the period when the hamster embryo is susceptible to a wide variety of teratogenic insults because the major embryonic differentiation of hamster organ systems is being accomplished. The levels of zinc found in embryonic tissue at 9 dg were very low and did not cause any appreciable developmental malformations.

Feaster *et al.* (1955) showed that, although absorption of zinc from the GI tract of rats is poor, zinc movement across the placenta to the fetuses is relatively free at all stages of gestation. Radiozinc concentration in organs paralleled total zinc values in maternal tissues, with the kidney showing the highest concentration, followed in order by the liver, pancreas and femur. Fetal content of zinc increased throughout the gestational period, reaching a peak at term.

Analyses by Casey and Robinson (1978) in 40 human fetuses of 22 to 43 weeks gestation found that zinc concentration was much higher in liver than in other tissues but decreased significantly with gestational age. Levels in skeletal muscle increased with age. None of the tissues appeared to store zinc; therefore, all zinc available to the fetus would be utilized.

Zinc content was determined in human placentas, maternal blood, and fetal blood by Baglan *et al.* (1974). These investigators

found that the concentrations in fetal blood were less than one-half those in maternal blood and the concentration in the placenta was about four times higher than that in fetal blood. Henkin *et al.* (1971) in their study of zinc concentrations in venous blood from 15 normal mothers and in the umbilical cords of their 15 normal babies found that absolute levels of free zinc in the pregnant woman at term remained unchanged from the nonpregnant state. However, they found lowered levels of total zinc in maternal serum at term primarily because of significant decreases in zinc binding proteins. Mean fetal serum zinc concentrations, both bound and free, were not significantly different from adult, nonpregnant levels.

Zinc and cadmium levels were determined in 36 human embryo/fetuses from 31 to 78 dg; 14 fetuses, ranging from 85 to 185 dg; and one 261 dg fetus. The mean concentration of zinc in four intact embryos aged 31 d was $2.8 \mu\text{g g}^{-1}$ wet tissue (range of 2.6 to $3.0 \mu\text{g g}^{-1}$) (Chabe *et al.* 1973). The mean concentration in the remaining 32 embryos (35 to 78 dg) was about $20 \mu\text{g g}^{-1}$ wet tissue (range of 12.3 to $27.1 \mu\text{g g}^{-1}$) with little difference seen at the different ages. From 31 to 36 d was a period of rapid growth: 72 mg average weight at 31 d to 120 mg at 36 d, but at the same time the zinc concentration increased about seven-fold. Chaube and her colleagues analyzed the liver, brain and kidney of the fetuses from the second trimester but did not analyze the kidney in the third trimester fetus. The mean concentration in the liver during the second trimester was $168 \mu\text{g g}^{-1}$ and in the one fetus from the third trimester was $118 \mu\text{g g}^{-1}$. The mean zinc concentration in the brain was $5.6 \mu\text{g g}^{-1}$ during the second trimester and $12 \mu\text{g g}^{-1}$ in the third trimester. Kidney concentrations averaged $16 \mu\text{g g}^{-1}$. The investigators saw no trend related to age, sex or stage of development in these organs.

Roedler (1987) assembled data from several sources and determined concentration ratios for zinc in maternal and fetal tissues. Representative ranges of values of the ratio for the chloride, citrate and sulfate are: total body 0.06 to 3.0, 0.14 to 0.48, 0.15 to 13.6; bone (femur) 0.67 to 2.2, 2.0, 0.09 to 3.1; and liver 0.45 to 4.3, 1.14, 1.09 to 1.31.

Estimates were made of radiation doses to the embryo/fetus from ^{65}Zn injected into a pregnant woman's transfer compartment (Sikov and Hui, 1996). This transfer gave cumulated dose values of about 50 to 200 μGy through term for administration of 37 kBq at all stages after organogenesis.

A.31 Gallium

The stable isotopes of gallium ($Z = 31$) and their abundances are ^{69}Ga (60.2 percent) and ^{71}Ga (39.8 percent). Radioisotopes ranging from ^{63}Ga to ^{76}Ga have been listed in tables of isotopes, but many of these have half-lives less than 1 h. ^{66}Ga has a half-life of 9.5 h; ^{67}Ga has a half-life of 3.26 d; ^{68}Ga has a half-life of 68.1 min; and ^{72}Ga has a half-life of 14.1 h.

A.31.1 Biological Information

No metabolic data are given for gallium in ICRP Reference Man (ICRP, 1975). Based on studies in rats where little or no gallium administered as chloride was absorbed from the GI tract, ICRP assigned a fractional absorption value from the GI tract of 0.001 for all compounds of the element (ICRP, 1981).

Studies on the distribution and retention of gallium have been performed in various species after intravenous, intramuscular and subcutaneous injection. Experiments on rats have shown that the distribution and retention of radioactive gallium in the body is greatly influenced by the total amount of stable gallium administered as carrier (Hayes *et al.*, 1965). In the presence of stable carrier, radioactive gallium is strongly concentrated in bone, whereas after intravenous injection of carrier-free radiogallium as citrate the radionuclide is much more diffusely distributed. The ICRP chose to use a metabolic model appropriate for carrier-free gallium, (ICRP, 1981).

A.31.2 Fetal/Placental Information

The ICRP (1987) used the biokinetic model given in MIRD Dose Estimate Report No. 2 (Cloutier *et al.*, 1973b) to estimate radiation doses to the nongravid uterus from clinically relevant gallium radioisotopes. These values can be used as an estimate of the radiation dose for the embryo/fetus from conception to two months of gestation.

Data collected in pregnant animals (Anghileri *et al.*, 1985; Lathrop *et al.*, 1992; Mahon *et al.*, 1973; Wegst, 1981; 1992) of several species (rabbits, rats and mice) were used with data from nonpregnant humans (Cloutier *et al.*, 1973b) to develop a biokinetic model for gallium in the pregnant human (Watson, 1992b). The results derived from this model show that the placental activity

was about 10 times the fetal activity with little decrease occurring after uptake.

This ratio appears to agree well with results of the various animal studies. The ratio of the fetal to maternal concentration of gallium immediately after injection at term would be about 0.85. Roedler (1987) indicated that reported ratios of activity concentrations for gallium ranged from 0.2 to 4.

Residence times calculated from the transfer rate constants were used to calculate absorbed dose estimates (Table A.3) for the human fetus at four periods of pregnancy (Watson, 1992b). The S values were derived from a mathematical model describing the nongravid uterus for early pregnancy (C[h]risty and Eckerman, 1987) and from mathematical models describing the uterus and fetus at the end of the first, second and third trimesters (Davis *et al.*, 1987; Watson, 1992a). The dose factors presented by Russell *et al.* (1997b) for ^{67}Ga are almost identical to those shown in Table A.3. They also indicate that 190 MBq is the amount of ^{67}Ga administered in typical nuclear medicine procedures, resulting in radiation doses ranging between 18 and 38 mGy.

A.32 Germanium

Germanium (Ge, Z = 32) has several stable isotopes; these isotopes and their abundances are ^{70}Ge (20.6 percent), ^{72}Ge (27.4 percent), ^{73}Ge (7.67 percent), ^{74}Ge (36.7 percent), and ^{76}Ge (7.67 percent). Radioisotopes ranging from ^{65}Ge to ^{78}Ge are listed in tables of isotopes, but many of these have half-lives less than 1 h and only ^{68}Ge , ^{69}Ge and ^{71}Ge have half-lives greater than 1 d. ^{68}Ge (physical half-life = 287 d) is the basis of a generator to produce ^{68}Ga , a positron emitter used in nuclear medicine studies.

Table A.3—Estimated absorbed doses for the fetus from intravenous administration of radioactive gallium citrate (mGy MBq^{-1}) (Watson, 1992b).

Target Organ	^{66}Ga	^{67}Ga	^{68}Ga	^{72}Ga
Embryo (0 through 2 months)	0.25	0.096	0.019	0.31
Fetus (end of first trimester)	0.21	0.16	0.012	0.21
Fetus (end of second trimester)	0.18	0.15	0.012	0.21
Fetus (at term)	0.17	0.13	0.012	0.19

No body content of germanium is given for Reference Man; however, the daily intake in food and fluids is estimated to be 1.5 mg (ICRP, 1975). Other data indicate that the body content is about 2 mg (ICRP, 1981). Dietary forms of germanium as well as orally administered GeO_2 are almost completely absorbed from the GI tract; therefore, the ICRP assigned a fractional absorption of one for all compounds of germanium (ICRP, 1981).

The only organ that has been found to have concentrations of germanium higher than that for a uniform distribution in the body is the kidney. The excess of germanium in the kidneys at early times after injection is thought to be attributed to the rapid excretion of the element in the urine (Durbin, 1960).

No information was located concerning placental transfer or biological disposition by the embryo/fetus.

A.33 Arsenic

The only stable isotope of arsenic (As, Z = 33) is ^{75}As . Radioisotopes ranging from ^{68}As to ^{85}As have been listed in tables of isotopes, but many of these have half-lives less than 1 h. Only ^{71}As to ^{74}As , ^{76}As and ^{77}As have half-lives greater than 1 d.

A.33.1 Biological Information

Arsenic is a natural constituent in the human body. The arsenic content of ICRP Reference Man (ICRP, 1975) is reported to be 18 mg with 0.1 mg in the skeleton. Other data indicate that the total body content of arsenic is probably not in excess of 10 mg and could be as little as 0.2 mg (ICRP, 1981). The absorption of arsenic from the GI tract is highly variable. Some compounds such as arsanilic acid and sodium or potassium arsenate have fractional absorption in pigs, cows and dogs of about 0.15 to 0.46. However, other compounds such as sodium arsenite and arsenic trioxide appear to be almost completely absorbed in rats (ICRP, 1981). In humans, arsenic administered as arsenic trichloride and dietary arsenic is almost completely absorbed from the GI tract (ICRP, 1981). The ICRP chose 0.5 as the fractional absorption from the GI tract for radiological protection purposes.

In humans, arsenic is uniformly distributed in the organs and tissues of the body with only nails and hair having concentrations substantially greater than the whole-body average (ICRP, 1981). The metabolism of the element is dependent upon chemical form

and animal species. The most extensive studies of arsenic metabolism in humans (Mealey *et al.*, 1959) are not compatible with the daily intake and total body content of stable arsenic given for Reference Man (ICRP, 1975).

A.33.2 *Fetal/Placental Information*

Pregnant mice were given 20 mg kg⁻¹ sodium arsenite by intraperitoneal administration or 40 mg kg⁻¹ by oral administration on gestation day 18 (Hood *et al.*, 1987). Arsenic distribution in maternal samples was essentially completed at 0.5 h. This was followed by uniform washout in the blood, kidney and urine over the remaining 24 h of the study, with a biological halftime of about 10 h. The rate of elimination from maternal samples was not influenced by administration route. For intraperitoneal administration, the peak concentrations of arsenic ($\mu\text{g g}^{-1}$) were 3.5 at 2 h in the fetus, 9.3 at 2 h in the placenta, 6.9 at 10 min in the blood, 712 at 1 h in the urine, 25.4 at 20 min in the kidney, and 7.9 at 0.5 h in the liver. From oral administration, the peak concentrations were 0.8 at 6 h in the fetus, 2.3 at 1 h in the placenta, 2.0 at 1 h in the blood, 342 at 2 h in the urine, 11.0 at 1 h in the kidneys, and 11.7 at 1 h in the liver. The higher concentrations in fetuses and placentas with intraperitoneal than with oral administration were presumably the result of slower uptake from the intestines than from the peritoneum, as well as the ability of the liver to intercept arsenic absorbed from the intestines and prevent its reaching the placental circulation rapidly.

Stable arsenic, as arsenic acid, and ¹²⁵Sb chloride were fed to mice from the day of conception (preimplantation period); then ⁷³As and ¹²⁵Sb were administered by intraperitoneal injection on day 12 (during organogenesis) with arsenic and antimony in the diet continuing throughout pregnancy (Gerber *et al.*, 1982). In animals killed from day two to six, concentrations of arsenic were 0.6 percent in liver, 0.34 percent in uterus, 0.23 percent in ovaries, 1.1 percent in thyroid, 0.2 percent in blood, 0.15 percent in brain, 0.23 percent in bone, 0.36 percent in skin, 0.18 percent in muscle. Significant changes occurred only in lung where the concentration decreased from 0.87 percent to 0.29 percent from day two to six and in brain where it decreased from 0.19 percent to 0.1 percent. For intraperitoneally administered arsenic, 95 percent of the material has a halftime of 6 h, and five percent has a halftime of 2.4 d. Arsenic was apparently rapidly removed from the intraperitoneal injection site and transferred to the kidney for excretion. Highest

concentrations occurred in kidney and intestine with high levels also in the lungs and spleen. When feeding of arsenic was ended, about 80.5 percent of the activity decreased with a halftime of 8.75 d and 19.5 percent with a halftime of 120 d. The retained arsenic passed readily into the fetus.

A.34 Selenium

The stable isotopes of selenium (Se, Z = 34) are ^{74}Se , ^{76}Se , ^{78}Se , ^{80}Se and ^{82}Se . Their abundances are ^{74}Se (0.87 percent), ^{76}Se (9.02 percent), ^{77}Se (7.58 percent), ^{80}Se (49.8 percent), and ^{82}Se (9.19 percent). Radioisotopes ranging from ^{70}Se to ^{87}Se are listed in tables of isotopes. Only ^{72}Se , ^{73}Se and ^{75}Se have half-lives greater than 1 h.

A.34.1 Biological Information

Selenium is a natural constituent of the human body. The selenium content of ICRP Reference Man (ICRP, 1975) is 13 mg, all of which is in soft tissues. Selenium in food is almost completely absorbed from the GI tract. However, elemental selenium and selenides appear to be relatively inactive biologically, and only a small fraction of these forms of selenium is absorbed during their passage through the GI tract. The ICRP assigned 0.05 as the fractional absorption from the GI tract for elemental selenium and selenides (ICRP, 1981) and the f_1 of 0.8 was again adopted for all other compounds of the element (ICRP, 1995).

Distribution and retention of various compounds of selenium have been studied in several mammalian species including humans. Furchner *et al.* (1975) determined retention of ^{75}Se in the mouse, rat, monkey and dog. Selenium metabolism is discussed in ICRP Publication 69 (ICRP, 1995) and the distribution and retention of selenomethionine in humans is reported in a MIRD committee pamphlet (Lathrop *et al.*, 1973). Intravenously injected selenium is concentrated in the liver, kidneys, pancreas and spleen. In studies with rats, biological halftimes for retention in all organs and tissues of the body were found to be similar (Furchner *et al.*, 1975). In humans, data indicate that a large fraction of the selenium deposited in the pancreas is lost with a biological halftime of about 1 d (Lathrop *et al.*, 1973). The whole-body retention of selenium in humans is described by three compartments with biological halftimes of 3 d (10 percent), 30 d (40 percent) and

200 d (50 percent) (ICRP, 1995). However, selenium retention in the body appears to be dependent upon the form of intake and the nature of the diet.

A.34.2 Fetal/Placental Information

Archimaud *et al.* (1992) fed ^{75}Se to pregnant rats and analyzed the placental transfer of the selenium into the fetuses. The concentration ratio of fetus to dam was 0.67 in animals killed at a gestational age of 13 d and 0.9 in animals killed at a gestational age of 20 d. The concentration ratio of placenta to dam was 1.7 at 13 d and 1.5 at 20 d. The main organs of retention in the fetus were the testis, kidney and liver.

A study with selenium selenite in pregnant mice showed that concentrations in the fetus were larger when selenium and methylmercury were administered together than when selenium was administered alone (Iijima *et al.*, 1978). At 48 h after administration of selenium alone, the concentration of selenium in the fetus had reached a plateau but continued to increase when methylmercury was administered with the selenium.

Sodium selenite was administered subcutaneously to a group of mice on day 12 of gestation and to another group on day 16 (Nishikido and Suzuki, 1985). The investigators found noticeable differences in distribution and placental transfer of selenium between the two stages of gestation. Selenium concentrations were higher in the liver, kidneys and lungs in the day 16 group than in the day 12 group, but even more impressive were the increased selenium concentrations as well as increased uptake percentages in the placentas and fetuses in the day 16 group compared with the day 12 group. The ratio of selenium concentration in the fetus to that in the placenta was significantly higher in the day 16 group than in the day 12 group which indicates that the placental barrier in transferring selenium from mother to fetuses was reduced or that the fetuses tended to accumulate more selenium on day 16. The fetal selenium concentrations remained unchanged up to 24 h, but in the maternal tissues the concentrations decreased during this period.

The data of Gaull *et al.* (1973) from humans are compatible with the hypothesis that amino acids, including L-methionine, generally are transferred from mother to fetus by active transport. The fetal plasma concentrations of methionine were consistently greater than the maternal plasma concentrations. Hilditch *et al.* (1973) studied uptake of ^{75}Se -selenomethionine by the fetus in eight

patients by evaluating the radioactivity in the babies and mothers 2 to 4 d after birth. The relative concentration of activity of baby to mother ranged from 1.6 to 2.7 with most of the ratios about 1.6 to 1.9. The mean level of uptake was 9.5 percent.

When 10 µCi of ^{75}Se -methionine was administered by infusion into 14 patients who were to undergo elective cesarean sections, Jandial *et al.* (1976) found that the ^{75}Se concentrations in the maternal blood, the uterine blood, and the retroplacental blood were approximately equal but the placental concentration was higher by approximately a factor of 10. When the activity was administered by bolus intravenous injection, all concentrations were approximately the same including the placenta.

Selenium content was determined in human placentas, maternal blood, and fetal blood by Baglan *et al.* (1974). These investigators found that the concentrations were not significantly different among the tissues studied. Selenium levels correlated with mercury values.

A.34.3 Radiation Dose Estimates

Hilditch *et al.* (1973) used an effective halftime of 67.5 d in the infant to calculate the radiation dose to the fetus from their uptake data. The whole-body dose was 3.5 mGy MBq⁻¹ at 30 weeks gestation and 1.76 mGy MBq⁻¹ for administration at term. The radiation dose to the mother was 2.43 mGy MBq⁻¹ when the same effective halftime was used.

Roedler (1987) compiled data from several sources to determine activity concentration ratios of the fetus to the mother. Although he gave no dose estimates, ratios of about 0.6 to 0.7 were found for most soft tissues, 0.9 for blood, and 1.7 to 9.2 for bones and teeth.

A.35 Bromine

The stable isotopes of bromine (Br, Z = 35) and their abundances are ^{79}Br (50.5 percent) and ^{81}Br (49.5 percent). Radioisotopes ranging from ^{74}Br to ^{90}Br are listed in tables of isotopes, but many of these have half-lives less than 1 h. Only ^{77}Br and ^{82}Br have half-lives that are greater than 1 d.

Bromine is a natural constituent in the human body. The bromine content of ICRP Reference Man (ICRP, 1975) is 200 mg with 170 mg in soft tissue. According to the ICRP (1980), almost all

orally administered bromine is absorbed from the GI tract, and they chose one as the fractional absorption.

Because the metabolic behavior of bromide in the human body is similar to that of chloride, the ICRP (1980) used the same metabolic model for bromine as for chlorine.

A.36 Krypton

There are six stable isotopes of krypton (Kr, Z = 36) in the range ^{78}Kr to ^{86}Kr , but ^{84}Kr accounts for 57 percent. Radioisotopes ranging from ^{74}Kr to ^{97}Kr have been listed in tables of isotopes, but many of these have half-lives less than 1 h. Three isotopes, ^{79}Kr , ^{81}Kr and ^{85}Kr have half-lives greater than 1 d.

A.36.1 Biological Information

Krypton is an inert gas and is not a natural constituent of the human body. The ICRP (1979) did not give a metabolic model for krypton because they considered the internal irradiation from an inert gas absorbed in tissue or contained in the lungs to be negligible in comparison with the external irradiation from a cloud of a radioactive noble gas. The assumption is made that all inert gases (krypton, xenon, radon, etc.) are similar in their biological behavior in the body. The NCRP made a compatible statement in Report No. 44 (NCRP, 1975), and provided substantial information on the physiochemical behavior in body compartments.

Noble gases are more soluble in lipids than in water; hence, tissues with high fat content concentrate more of the gas than do other tissues. If the gas is uniformly distributed in body fat, the concentration can be obtained by dividing the activity by the mass of the fat content of the body (12,500 g) and multiplying by the fractional fat content of the organ or tissue of interest. Because of unequal blood perfusion rates, the gas distribution among the fatty tissues will not be uniform. Higher ratios will be attained in organs such as brain, adrenals and gonads which have relatively high blood perfusion rates.

A.36.2 Fetal/Placental Information

Several studies with krypton gas have been performed in pregnant animals. Bergeron *et al.* (1973) studied placental transfer of inert gases by administering ^{85}Kr on 17 dg to pregnant rats *via a*

catheter in the left iliac artery. Samples were taken at 5, 15, 30, 45 and 60 s after injection. The distribution of krypton in the uterus was not uniform. The placenta contained regions of relatively high amounts of radioactive material and regions almost devoid of radioactivity. The regions corresponding to the fetus showed no radioactivity during the period of the study. According to these investigators, at 60 s after injection, a substantial amount of oxygen or bicarbonate was transferred to the fetus; however, oxygen is transferred as plasma-bound gas, CO_2 as bicarbonate dissolved into the plasma, and noble gases such as krypton and xenon as gas attached to plasma lipids. The authors postulated that because the gas is dissolved into plasma lipids it must reach an equilibrium in maternal plasma before it can reach the placenta to be transferred. The rate of transfer corresponding to that of lipids would be slower and would occur by pinocytosis and not by diffusion.

Andrew *et al.* (1978) investigated the kinetics of inhaled krypton in the blood of pregnant ewes and their fetuses. The ewes were exposed for approximately 1.5 h until equilibrium concentrations in maternal blood and in most other tissues were approximately (37 Bq g^{-1}). Concentrations dropped to 10 percent of the maximum in the maternal artery about 9 min after exposure ceased, in the maternal vein about 32 min after exposure ceased, and in the fetal artery about 60 min after exposure ceased. They found few differences between the fetal and maternal concentrations except for lung and adipose tissues which serve as a depot for krypton. The high level of krypton found in the adult lung in this study was caused by occluding the airway after the last breath to contain the krypton exposure atmosphere. Concentrations of ^{85}Kr in fetal fat from pericardial and subcutaneous sites were markedly lower than in adult fat. The ^{85}Kr concentration in placental samples was significantly higher than in any fetal tissues.

Pregnant rats at 7 to 12 or 12 to 17 dg were exposed continuously for five consecutive days to ^{85}Kr atmospheres at 1.48 GBq L^{-1} to determine the embryotoxicity of ^{85}Kr (Andrew *et al.*, 1979). The radiation dose to the skin of the dams was high enough to produce erythema and other signs of radiation toxicity; however, histopathological examinations of maternal lungs revealed no evidence of radiation-induced pathology at 9 to 14 d after initiation of exposures that produced an estimated lung dose of 30 Gy. The distribution of krypton was essentially the same as that in studies performed with approximately 1,000 times less activity. No evidence of increased intrauterine mortality nor of external or skeletal malformations were seen in the exposed fetuses. The only

significant embryotoxic effect observed was decreased fetal weight which was probably secondary to effects of the exposure on the dam's nutrition.

A.36.3 *Radiation Dose Estimates*

Sikov and Hui (1996) developed approaches to fetal dosimetry estimations for noble gases breathed by a pregnant woman for various lengths of time. The radiation absorbed doses to the fetus were calculated to be 19 mGy for a 24 h exposure to a nominal atmosphere of 37 kBq mL⁻¹ of ⁸⁵Kr. The dose during embryonic stages was about twice this value.

A.37 Rubidium

The stable isotopes of rubidium (Rb, Z = 37) and their abundances are ⁸⁵Rb (72 percent) and ⁸⁷Rb (28 percent). Radioisotopes ranging from ⁷⁹Rb to ⁹⁵Rb are listed in tables of isotopes, but many of these have half-lives less than 1 h. Only ⁸³Rb, ⁸⁴Rb and ⁸⁶Rb have half-lives greater than 1 d.

A.37.1 *Biological Information*

Rubidium is a natural constituent in the human body and the content of Reference Man (ICRP, 1975) is 0.68 g with 0.47 g in soft tissue. Rubidium is often used as a substitute for potassium in physiological studies and is assumed to share the same transport mechanism (Dancis *et al.*, 1983). According to Lloyd *et al.* (1973), rubidium is almost totally absorbed from the GI tract and the ICRP chose one as the fractional absorption from the GI tract (ICRP, 1980).

Rubidium is approximately uniformly distributed among the organs and soft tissues of the body. The exception is mineral bone where the concentration is about three times the average whole-body concentration (ICRP, 1975). Rubidium in bone is assumed to be uniformly distributed throughout the mineral matrix. Biological half-lives in the total body are 5 d for five percent and 60 d for 95 percent (ICRP, 1987).

A.37.2 Fetal/Placental Information

Rubidium content was determined in human placentas, maternal blood, and fetal blood by Baglan *et al.* (1974). These investigators found that the concentrations in the maternal and fetal blood were approximately equal but the concentration in the placenta was about 50 percent higher.

A study with human term placenta by Dancis *et al.* (1983) found that the uptake of ^{86}Rb by perfused placental fragments was rapid, yielding high intracellular concentrations that had not reached equilibrium by the end of the study. They concluded that the rubidium diffuses passively through the same channels that are used by other small water-soluble molecules such as urea, sodium and chloride.

Intravenously injected ^{86}Rb is nearly 100 percent extracted after 20 s in every organ but the lung, liver and brain (Saperstein, 1958). Boda *et al.* (1971) used this as the basis for their study of blood flow with ^{86}Rb . With the exception of the parenchymal organs, significant changes occurred in the blood distribution of the individual organs in the fetus and in the normal living and hypoxic newborn.

Estimates of cumulated radiation dose are in the range of 0.02 to 0.1 mGy for administration of 37 kBq of ^{86}Rb (0.5 to 3 mGy MBq $^{-1}$) at various times of gestation (Sikov and Hui, 1996).

A.38 Strontium

The stable isotopes constitute 93 percent of strontium (Sr, Z = 38); they are ^{84}Sr , ^{86}Sr , ^{87}Sr and ^{88}Sr . Radioisotopes range from ^{80}Sr to ^{95}Sr but only ^{82}Sr , ^{83}Sr , ^{85}Sr , ^{89}Sr and ^{90}Sr have half-lives greater than 1 d.

A.38.1 Biological Information

The strontium content of ICRP Reference Man (ICRP, 1975) is 0.32 g; almost all is in the skeleton and soft tissues contain only 3.3 mg. Both human and animal data suggest that the fractional uptake of dietary strontium and of soluble salts from the GI tract is in the range of 0.2 to 0.5. The ICRP (1979) chose 0.3 as the fraction absorbed from the GI tract for soluble salts of strontium; this value was adopted again by the NEA/OECD (1988b) and the ICRP (1993).

Strontium is an alkaline earth with metabolic behavior that is similar to calcium although it usually is less readily transported. The ICRP Task Group on Alkaline Earth Metabolism in Adult Man developed a comprehensive model for the retention of strontium in adults. This model was revised in ICRP Publications 56 and 67 (ICRP, 1989; 1993), which present detailed metabolic models for adults and children.

A.38.2 *Fetal/Placental Information*

The placental transfer of strontium and, particularly, the ratio of calcium-to-strontium transfer have been studied in several animal species. In metabolic studies with pregnant mice, Pecher and Pecher (1941) found that part of the calcium and strontium previously fixed in the skeleton of the mother migrated to the fetus during the last days of pregnancy. The amount of calcium in the fetuses was much greater than the amount of strontium.

When ^{89}Sr was administered to mice before or during pregnancy (Finkel, 1947), the strontium readily passed from mother to fetus. However, the total amount of strontium found in the young at birth varied directly with their weights and inversely with the length of time from treatment of the mother to delivery when that time exceeded 3 d. The fetal-to-maternal concentration ratio of strontium was also dependent on the number of days between injection and delivery. In young born 1 to 4 d after administration to the mother, the mean concentration ratio was 1.91. For intervals of 5 to 20 d, the ratio decreased rapidly and then remained at about seven percent when administration preceded conception. The amount of strontium in the offspring born 20 or more days after administration to the mother appeared to depend on the amount of strontium present in the mother's bones. The amount of strontium in the mothers immediately after parturition closely approximated the retention by nonpregnant animals. In nonpregnant animals the strontium was lost by excretion through the urine and the feces, but in pregnant animals as much as 75 to 80 percent of the total amount lost from the dams was in the litters.

Kidman *et al.* (1951) injected pregnant rabbits with $^{90}\text{Sr} - ^{90}\text{Y}$ approximately 24 h, 9 d, and 38 to 50 d before delivery. Only the fetuses from the animals injected 24 h before delivery had concentrations of strontium greater than those in the mothers (four to eight times). For animals injected 9 d before delivery, the mean concentration ratio was 0.76; for animals injected 38 to 50 d before delivery, the ratio was about 0.03. A study in rats by Ruhmann

et al. (1963) showed that the gestational age at injection was the most important factor in governing fetal retention of strontium received through the placenta. Litters from dams injected on the 19th gestational day contained three times the fractional amount of strontium as those injected on day 17 and 16 times that in animals injected on day 15. The dams retained less strontium and excreted larger quantities through the kidneys than did the non-pregnant rats. Levels of strontium transferred to the fetus and retention in the placenta were found by Moskalev *et al.* (1969) to depend primarily on chemical characteristics and period of pregnancy. The placental transfer of strontium in rats, rabbits, sheep and cows increased 20-fold between midterm and the end of pregnancy. Strontium-85 was administered by intraperitoneal injection to rats at various times before and after conception (Stather *et al.*, 1987). The concentration ratio of fetus to mother at time of birth for activity administered 28 d before conception was 0.03, on gestation day 2 was 0.06, on gestation day 13 was 0.21, and on gestation day 19 was 5.3.

Continuous feeding experiments with rats on a ^{90}Sr -labeled diet indicated that dietary calcium was utilized for bone growth by a factor of 3.6 over strontium; about 29 percent of the fetal calcium was derived from maternal calcium; dietary calcium was utilized for bone formation in the developing fetus by a factor of 5.1 over strontium (Comar *et al.*, 1955). Wassermann *et al.* (1957) also studied the discrimination of calcium over strontium in the placentas in rats and rabbits. They found that transfer across the placenta was about twice as great for calcium as for strontium. The fetal content of ^{45}Ca in the rat was 2.8 percent and of ^{85}Sr 1.3 percent. The placental discrimination in the rabbit was somewhat greater than that in the rat but, in both, the placental transfer of strontium from dam to fetus is about one-half that of calcium.

According to Holmberg *et al.* (1960), the ability of the mouse fetus to take up ^{90}Sr appeared after the 14th dg, and the uptake continued for more than 4 h after injection of the mother. They also found that ^{90}Sr injected intraperitoneally into the mother was available to the fetus in undiminished quantity for at least four weeks. At 14 dg in rats, Schulert *et al.* (1969) found that the placenta contained about 25 percent less strontium than calcium, but at 20 d the placenta retained about 22 percent more strontium than calcium. The concentration of strontium in the fetus increased from 0.098 percent injected activity per gram at 14 dg to 0.103 percent at 17 dg and to 0.14 percent at 20 dg.

The transport of radiostrontium across the primate placenta appears to be bidirectional. A study in pregnant rhesus monkeys with ^{85}Sr injected into the fetal circulation and ^{90}Sr injected into the maternal femoral vein showed that twice as much ^{85}Sr was recovered in the mother's body as in the fetus when the nuclide was administered to the fetus (MacDonald *et al.*, 1962). The fetus and placenta contained 43 percent of the ^{85}Sr and 12 percent of the ^{90}Sr . The concentration of strontium was greater in fetal bone than in maternal bone. The ratio of ^{85}Sr concentration in fetal/maternal bone was about 20:1, and the ^{90}Sr concentration ratio was about 3:1. The pattern of strontium accumulation in bone tissue was the same for both radionuclides. Even when new mineral was laid down, the ratio of accumulation in callus compared to accumulation in intact bone was the same for ^{85}Sr as for ^{90}Sr .

Concentrations of ^{89}Sr in pregnant mice and their fetuses were compared in several soft tissues and bone (Jacobsen *et al.*, 1978). The ratios of strontium concentrations in fetal-to-maternal organs for activity administered on day 17 of gestation and killed on day 20 were: liver 4.9, kidney 12, heart 1.1, brain 1.5, calvaria 1.6, and long bones 5.0.

Studies in the human include those of Rivera (1963), who measured strontium in maternal and newborn blood serum to determine the strontium-calcium discrimination by the placenta. However, no clear determination was made because the ratio of the calcium concentration in these tissues was not known. Twardock (1967; Twardock *et al.*, 1969) had seen a gradual decrease in placental discrimination of the guinea pig against strontium throughout gestation. No abrupt change that might be associated with loss of any of the placental tissue layers was seen, and calcium was transferred selectively over strontium even at the end of gestation. If discrimination by the human placenta decreases during pregnancy, this might explain Rivera's results.

In a review of literature on strontium metabolism in pregnancy and strontium transfer across the human placenta, Griessl (1987) drew several conclusions. The rapid growth of the fetal and neonatal skeleton with its high proliferation of bone cells and the development of the hematopoietic system, which start about the fifth month *in utero*, cause the skeleton to be more sensitive to radiation from strontium than at any other stage of life. Strontium taken in before pregnancy is not available to any great extent for transfer to the fetus. The total amount of strontium in the developing skeleton increases about 20-fold in the course of pregnancy. During the last four weeks before birth the fetal skeleton accumulates the same

amount of strontium as during all of the preceding months of pregnancy. In the sixth month of pregnancy about 6 to 10 percent of ingested strontium is transferred to the placenta, but in the final month this value reaches 10 to 17 percent. Although strontium follows the calcium pathways in the body, the metabolic processes can discriminate against strontium in favor of calcium; however, the ability of placental membranes to discriminate against strontium decreases during pregnancy. By the end of pregnancy this ability to discriminate has almost disappeared and strontium is passed on to the fetus at nearly the same Sr/Ca ratio as that present in the maternal circulation. Griessl also pointed out that although strontium was shown to pass the placenta bidirectionally by MacDonald *et al.* (1962), the placental net flux is mainly a unidirectional transfer by means of active processes. Also the studies of GI absorption of Ca/Sr may be relevant to understanding placental transfer of these elements.

Taylor and Bligh (1992) measured transfer of alkaline earth metals in rats and found that the transfer ratios for passage across the placenta do not differ significantly from those for GI transfer. The transfer ratios for strontium ranged from about 0.3 to 0.4 for placental transfer and GI transfer.

A.38.3 Radiation Dose Estimates

Roedler (1987) used fallout measurements and other available data to estimate radiation doses to the fetus from ^{90}Sr . For intake at six months of pregnancy, the fetal dose was 0.22 Gy MBq^{-1} while for intake at nine months, the fetal dose was 0.67 Gy MBq^{-1} taken in by the mother. The ratio of bone doses in fetus to those in the adult was 0.1 for intake at six months and 0.3 for intake at nine months. Stather *et al.* (1992) used human data and a Ca:Sr discrimination ratio of 1:0.5 to estimate radiation doses to the mother and the fetus from chronic ingestion of strontium by the mother during the course of pregnancy. The committed effective dose for the fetus from ^{85}Sr was $1.5 \times 10^{-8} \text{ Sv Bq}^{-1}$, and the ratio of committed effective dose of fetus to that of the mother was 0.85.

Mays and Lloyd (1966) estimated the lifetime radiation dose to the infant skeleton from a single ingestion by the mother of 37 kBq ^{90}Sr at six months of gestation to be 6 mGy and 18 mGy if the ingestion is at nine months. The lifetime skeletal radiation dose to an infant from 37 kBq of ^{89}Sr is 1.5 mGy for an ingestion at six months and 1.6 mGy for an ingestion at nine months.

Radiation absorbed doses and dose rates for ^{89}Sr and ^{90}Sr in equilibrium with ^{90}Y introduced into the mother's blood at several stages of gestation have been estimated by Sikov and Hui (1996). Doses from ^{89}Sr were calculated for different periods after intake, but overall cumulated doses to term were about 10 to 50 μGy per 37 kBq following injection at any time after three months of gestation; corresponding doses from $^{90}\text{Sr} - ^{90}\text{Y}$ were about three times as great.

A.39 Yttrium

The only stable isotope of yttrium ($\text{Y}, \text{Z} = 39$) is ^{89}Y but there are over 20 radioisotopes, ranging from ^{82}Y to ^{96}Y . Many of these have half-lives less than 1 h although the isotopes ^{87}Y , ^{88}Y , ^{90}Y and ^{91}Y have half-lives greater than 1 d.

A.39.1 Biological Information

ICRP Publication 23 (ICRP, 1975) does not give total body content or normal daily intake of yttrium of Reference Man. However, the total liver content is stated as 1.6 mg and the total trabecular bone content as less than 4.5 mg. Because studies in rats and dogs have detected little uptake of yttrium from the GI tract, the ICRP (1980) chose 1×10^{-4} as the fractional absorption. The metabolism of yttrium is described in ICRP Publication 30 (ICRP, 1980).

A.39.2 Fetal/Placental Information

Kriegel and Weber (1961) studied the dependence of placental turnover of yttrium in rats on 19 dg when the yttrium was administered both before and during the gestation period. They found a statistically significant positive correlation between the amounts of radionuclide deposited in the embryo and the mass of the embryo. However, placental turnover was found only when the incorporation through the mother occurred during the last quarter of the gestation period. At this later stage of pregnancy, the ratio of the concentration in the placenta to that in the fetus was approximately 30.

As described in Section A.38.2 on strontium, Kidman *et al.* (1951) injected rabbits with $^{90}\text{Sr} - ^{90}\text{Y}$ at various times before or during gestation. The ^{90}Y was approximately in radioactive equilibrium with the ^{90}Sr in the mothers' bones and in the fetuses.

A.40 Zirconium

There are five stable isotopes of zirconium (Zr , $Z = 40$); the most abundant is ^{90}Zr (51.5 percent). The abundances of the others are ^{91}Zr (11.2 percent), ^{92}Zr (17.1 percent), ^{94}Zr (17.4 percent), and ^{96}Zr (2.8 percent). Radioisotopes ranging from ^{81}Zr to ^{99}Zr are listed in tables of isotopes, but many of these have half-lives less than 1 h. Only ^{88}Zr , ^{89}Zr , ^{93}Zr and ^{95}Zr have half-lives greater than 1 d. Because it is activated by neutron bombardment of reactor fuel cladding, 64 d half-life ^{95}Zr and its daughter ^{95}Nb are important.

A.40.1 Biological Information

Zirconium is a natural constituent of the human body and the content of Reference Man is 420 mg (ICRP, 1975). Fletcher (1969) found that the fractional GI absorption of various zirconium compounds in rats varied from 0.0003 to 0.002. The ICRP (1979) adopted 0.002 as the fractional absorption for all zirconium compounds; this was later revised to 0.01 (NEA/OECD, 1988b; ICRP, 1989).

Studies on zirconium are reviewed in ICRP Publications 30 and 56 (ICRP, 1979; 1989), which present discussions of its metabolism. Based on animal studies, it appears that bone contains most of the body zirconium.

A.40.2 Fetal/Placental Information

In a study of ^{95}Zr and ^{95}Nb distributions in maternal and fetal rabbit tissues, MacDonald *et al.* (1965b) found that zirconium crossed the placental membrane into the rabbit fetus after introduction of carrier-free oxalates into the maternal blood. Most zirconium in the mother and the fetus was found in the bone with concentrations from 5 to 20 times greater than in other tissues. Placental tissue had a much lower concentration of zirconium than bone but was similar to maternal soft tissues.

Studies in rats yielded comparable results (Fletcher, 1969). Likewise, in late-gestation mice, autoradiographic evaluations showed some early retention in placenta that was followed by transfer to the fetus with deposition in bone, but concentrations in yolk sac remained high.

A.41 Niobium

The only stable isotope of niobium ($\text{Nb}, Z = 41$) is ^{93}Nb , but there are about 20 radioisotopes, ranging from ^{88}Nb to ^{101}Nb . Many have half-lives less than 1 h but several (^{91m}Nb , ^{92m}Nb , ^{93m}Nb , ^{94}Nb , ^{95}Nb and ^{95M}Nb) have half-lives longer than 1 d. Of interest is ^{95}Nb , which is the daughter of ^{95}Zr and has a half-life of 35 h.

A.41.1 Biological Information

Niobium is a natural constituent of the human body and the content of Reference Man (ICRP, 1975) is 110 mg, all of which is in the soft tissue. The f_1 value of 0.01 for all compounds of niobium given in Publication 30 was again adopted in Publication 56, which also extended the discussion of its metabolism (ICRP 1979; 1989).

Studies of the metabolism of niobium in the mouse, rat, monkey and dog include those by Cuddihy (1978), Fletcher (1969), Furchner and Drake (1971), and Backström *et al.* (1967). The resulting ICRP model (ICRP, 1989) considers preferential retention of niobium in mineral bone (40 percent) with 20 percent in liver, 3 percent in kidney, and 37 percent in all other tissues. All organs and tissues appear to lose niobium at about the same rate, given as the sum of two exponentials having halftimes of 6 d (50 percent) and 200 d (50 percent).

A.41.2 Fetal/Placental Information

In their study of ^{95}Zr and ^{95}Nb distributions in maternal and fetal rabbit tissues, MacDonald *et al.* (1965b) found that niobium crosses the placental membrane into the rabbit fetus after introduction of carrier-free oxalates into the maternal blood. Most of the niobium in the mother was reported to be in the liver and kidney (but not bone) while most of the niobium in fetal tissues was found in the liver and bone. The placental tissue also contained a high niobium concentration.

The results obtained in mice by Backström *et al.* (1967) with ^{95}Nb were similar to the autoradiographic patterns with ^{95}Zr . Fletcher (1969) also obtained similar results with the two radionuclides, but there was greater placental transfer of niobium than of zirconium. Quantitatively, however, placental concentrations of ^{95}Nb were measured as being 10- to 100-fold greater than in the fetus on the day after administration to rats at 18 to 20 dg but fetal bone had the greatest concentrations (Schneidereit *et al.*, 1985).

Roedler (1987) used available data, including those of MacDonald *et al.* (1965b), to determine concentration ratios for niobium in maternal and fetal tissues. A range of values, 0.19 to 0.28, was calculated for total body, 0.005 to 0.12 for blood, spleen and kidney, 0.02 for liver, 0.1 to 0.62 for femur. In contrast the values were 91 to 105 for the tibia.

A.42 Molybdenum

There are seven stable isotopes of molybdenum (Mo, Z = 42), ^{92}Mo to ^{100}Mo ; abundances range from 9 to 24 percent. Radioisotopes range from ^{88}Mo to ^{105}Mo , but many have half-lives of less than 1 h. Only ^{99}Mo has a half-life greater than 1 d (65.9 h). This radioisotope is used as the basis for a generator to produce $^{99\text{m}}\text{Tc}$ for use in nuclear medicine and may be present as a contaminant in $^{99\text{m}}\text{Tc}$ -labeled radiopharmaceuticals.

The trace-element molybdenum is a natural constituent of the human body with a content of 9.5 mg in Reference Man (ICRP, 1975). Although results are variable, MoS_2 is poorly absorbed from the GI tract but salts of molybdic acid are readily absorbed. The ICRP chose 0.05 as the fractional absorption for MoS_2 and 0.8 for all other compounds of the element (ICRP, 1979). A value of one was later adopted for dietary molybdenum (ICRP, 1993).

As described in ICRP Publication 67 (ICRP, 1993), the model assumes that 10 percent of molybdenum in blood is deposited in skeleton and retained with a 10,000 d halftime. It is also assumed that 60 percent goes to general soft tissues, 25 percent to liver, and 5 percent to kidney. Retention times of 1 d (10 percent) and 50 d (90 percent) are assumed.

Regulatory limits state that the eluate from $^{99\text{m}}\text{Tc}$ generators must not contain more than 0.19 MBq of ^{99}Mo . Shearer and Pezzullo (1986) examined the dosimetry of some $^{99\text{m}}\text{Tc}$ radiopharmaceuticals contaminated with ^{99}Mo . Measurements began 10 to 14 d after administration of the $^{99\text{m}}\text{Tc}$ -labeled compound so that administered $^{99\text{m}}\text{Tc}$ had decayed leaving only $^{99\text{m}}\text{Tc}$ produced from the decay of ^{99}Mo . The only detectable ^{99}Mo was found in the liver. The biological halftime for the ^{99}Mo was estimated to be 6 d although adequate fits to the data were difficult to obtain because of the lack of early measurements.

A.43 Technetium

Technetium (Tc, Z = 43) has no stable isotope, but it has several radioisotopes ranging from ^{92}Tc to ^{107}Tc . Many of these have lives of less than 1 h, but only ^{95m}Tc , ^{96}Tc , ^{97}Tc , ^{97m}Tc , ^{98}Tc and ^{99}Tc have half-lives greater than 1 d. The most important isotope is ^{99m}Tc , which is a component of the majority of radiopharmaceuticals used for diagnostic nuclear medicine. This isotope, which has a 6 h half-life, is eluted in the form of pertechnetate from $^{99}\text{Mo}^{99m}\text{Tc}$ generators. The pertechnetate can be administered directly to patients or used to label other compounds. The labeled compounds have different distribution and retention patterns in the body with resulting differences in the radiation absorbed doses.

A.43.1 Biological Information

The fractional absorption of technetium as pertechnetate from the GI tract was reported by Beasley *et al.* (1966) to be about 0.95, but Hays (1973) has shown that the absorption of pertechnetate from an oral intake is extremely variable in timing and extent. The ICRP (1980) chose 0.8 as the fractional absorption for all compounds of technetium for radiation protection purposes. This value was considered to be too large for some technetium-labeled compounds and an f_1 value of 0.5 was adopted in ICRP Publication 67 (ICRP, 1993).

When administered intravenously as pertechnetate, technetium is concentrated primarily in the thyroid, GI tract, and liver (Harper *et al.*, 1964; McAfee *et al.*, 1964; Hays, 1973). A description of the distribution of pertechnetate at early times after intravenous administration requires a multicompartmental model (Hays and Berman, 1977). The simple model for the distribution and retention of pertechnetate that the ICRP (1980) earlier chose was again adopted in Publication 67 (ICRP, 1993). This may not be adequate for many of its compounds and models for a number of other technetium-labeled compounds, especially radiopharmaceuticals, are described in ICRP Publication 53 (ICRP, 1987).

A.43.2 Fetal / Placental Information

Organ distribution of several ^{99m}Tc -labeled radiopharmaceuticals was studied in pregnant rabbits (Mahon *et al.*, 1973). At 1 h after administration the ratio of ^{99m}Tc -pertechnetate in a single placenta to that in a single fetus was 0.22 and of placenta to blood

was 0.037; the ratio of ^{99m}Tc -polyphosphate in a single placenta to that in a single fetus was 10 and of placenta to blood was 0.005; and the ratio of ^{99m}Tc sulfur colloid in a single placenta to that in a single fetus was 10 and of placenta to blood was 0.0565.

Cumulated activity estimates for ^{99m}Tc -pertechnetate have been determined from biodistribution data from nonpregnant and pregnant rats studied at 13, 15, 17, 19 and 21 d gestation (Wegst *et al.*, 1983). The fetal activity per unit weight of tissue was not constant over the gestational ages studied. A maximum value of 6.7 Bq $\text{h}^{-1} \text{g}^{-1}$ occurred on 13 dg, falling by a factor of 2.5 at midterm and rising again at term to 5.07 Bq $\text{h}^{-1} \text{g}^{-1}$. The placental tissue concentration remained essentially constant over time with an average value of 25 Bq $\text{h}^{-1} \text{g}^{-1}$.

The effects of perchlorate on the quantitative distribution patterns of ^{99m}Tc sodium pertechnetate intravenously administered as pertechnetate in the adult and its fetus were studied by Lathrop (1976). At 1.5 h after administration the concentration ratio of technetium in the placenta to that in the blood was 2.1 without perchlorate and 0.49 with perchlorate pretreatment. The ratio of ^{99m}Tc with perchlorate to that without perchlorate was 0.34 in the placenta and 0.32 in the fetus.

A 32 week pregnant patient was studied with ^{99m}Tc -HMPAO to confirm fetal brain death (Maguire *et al.*, 1990). A focal fetal accumulation was seen in an image of the patient's abdomen. A region of interest yielded an estimate of 4.5 percent of the activity found in the maternal liver. After delivery, the infant was imaged to determine the localization of the ^{99m}Tc . Most of the activity was present in the liver, and no significant cerebral concentration was found. The diminished uptake in the fetal brain may be related to the immaturity of glutathione metabolism in the fetus or may result from the fact that about 50 percent of the umbilical venous blood returning to the fetus from the placenta passes through the fetal liver.

A.43.3 Radiation Dose Estimates

Roedler (1987) used available data to determine concentration ratios for technetium pertechnetate in maternal and fetal tissues. He obtained extreme ranges such as 0.04 to 4.8 in total body and 1.7 to 7.1 in femur but gave no dose estimates.

He also used available data to derive concentration ratios for several other technetium-labeled compounds. The C_F/C_M for technetium-labeled DTPA in the total body was 0 to 0.05, for colloids

0.002 to 0.11, for polyphosphate 0.006 to 0.018, and for pyrophosphate 0.0038 to 0.05. For technetium-labeled human serum albumin the C_F/C_M for plasma was 0.025 to 0.051.

Wegst (1992) extrapolated data for ^{99m}Tc pertechnetate collected in pregnant rats (Wegst *et al.*, 1983) to calculate radiation absorbed dose estimates for the human. She calculated that the mean fetal dose for the first two months of gestation would be $86 \mu\text{Gy MBq}^{-1}$ administered to the mother. She also presented results of biodistribution studies of ^{99m}Tc DTPA in pregnant rats and cumulated activities for the nonpregnant and pregnant animals at different stages of pregnancy (Wegst, 1992). The "equivalent time" factor suggested by McAfee and Subramanian (1981) was used to extrapolate to humans from the animal time base. The mean absorbed dose received by the human fetus during early pregnancy as extrapolated from the animal data was estimated to be $8.2 \mu\text{Gy MBq}^{-1}$ of ^{99m}Tc DTPA administered to the mother.

Sastray *et al.* (1976) published data for radionuclides used in placentography. The time-integral of activity (hours per gram of tissue) for ^{99m}Tc human serum albumin during the 30th week of pregnancy is 0.00014 in maternal whole body, 0.00094 in maternal blood, 0.0016 in fetal whole body, 0.000033 in fetal blood, and 0.00075 in fetal thyroid. The metabolic behavior and radiation dosimetry of ^{99m}Tc human serum albumin in pregnancies of 32 weeks gestation or later were studied by Herbert *et al.* (1969). Table A.4 summarizes these results.

Hedrick *et al.* (1988) observed the uptake of ^{99m}Tc methylene diphosphonate in the fetuses of two patients undergoing bone scintigraphic procedures. They estimated the radiation dose to an eight week old fetus to be $4.6 \mu\text{Gy MBq}^{-1}$ administered to the mother and

Table A.4—Radiation absorbed dose estimates for ^{99m}Tc human serum albumin (mGy MBq^{-1} administered to the mother).

Target Tissue	Sastray <i>et al.</i> (1976)	Herbert <i>et al.</i> (1969)
Maternal whole body	0.0046	0.0046
Maternal blood	0.013	0.012
Maternal gonads	0.010	0.010
Fetal whole body	0.0057	0.0032
Fetal blood	0.0046	0.0032
Fetal thyroid (unblocked)	0.012	0.0076

to an 18 week old fetus to be $2.6 \mu\text{Gy MBq}^{-1}$ by assuming that no activity entered the fetus and that most of the dose was from the activity in the urinary bladder of the mother.

Fetal absorbed dose estimates for pulmonary studies in the mother with ^{99m}Tc MAA and ^{99m}Tc DTPA aerosol have been made for different stages of pregnancy (Ponto, 1986). The dose estimate for the fetus from ^{99m}Tc MAA at all gestational ages was $2.2 \mu\text{Gy MBq}^{-1}$ administered to the mother. The estimates calculated by Ponto for ^{99m}Tc DTPA aerosol are shown in Table A.5.

Retention times, dose factors, and doses were estimated and are given in Russell *et al.* (1997a; 1997b). These are based on surveys of users and employ the newly revised stage-related pregnant woman phantoms and MIRDOSE 3 (Stabin, 1996; Stabin *et al.*, 1995). These evaluations emphasized several ^{99m}Tc -labeled radiopharmaceuticals that are most relevant to the embryo/fetus. These results are summarized in Table A.6.

A.44 Ruthenium and Rhodium

The six Group VIII metals of the fifth and sixth period of the periodic table, which are usually found mixed together in the uncombined state, are often referred to as the platinum metals. They are all high density, high melting point, and poorly-reactive elements that resemble each other chemically. Because of the differing atomic numbers and the radiological aspects of their radioisotopes, the elements of the fifth period [ruthenium (Ru, Z = 44),

Table A.5—Absorbed dose estimates for the fetus from inhalation of ^{99m}Tc DTPA aerosol by mother (Ponto, 1986) (mGy MBq^{-1} administered to the mother).

Gestational Age (month)	Fetal Dose
1	0.011
2	0.0077
3	0.0058
4	0.0038
5	0.0023
6	0.0020
7	0.0014
8	0.0013
9	0.0011

Table A.6—*Gestational-stage-related cumulated radiation doses (mGy MBq⁻¹) to the embryo/fetus following intravenous injection of ^{99m}Tc-labeled radiopharmaceuticals commonly used in women of childbearing age (after Russell et al., 1997b).*

Radio-pharmaceutical	Cumulative Radiation Dose (mGy MBq ⁻¹)				Typical MBq Administered
	Embryo	3 Months	6 Months	9 Months	
Pertechnetate	1.1E-02	2.2E-02	1.4E-02	9.3E-03	100-1,100
Disofenin ^a	1.7E-02	1.5E-02	1.2E-02	6.7E-03	350
DMSA ^b	5.1E-03	4.7E-03	4.0E-03	3.4E-03	220
DTPA ^b	1.2E-02	8.7E-03	4.1E-03	4.7E-03	750
DTPA aerosol	5.8E-03	4.3E-03	2.3E-03	3.0E-03	40
GHA ^b	1.2E-02	1.1E-02	5.3E-03	4.6E-03	750
HDP ^b	5.2E-03	5.4E-03	3.0E-03	2.5E-03	750
HMPAO ^{a,b}	8.7E-03	6.7E-03	4.8E-03	3.6E-03	750
HSA ^{a,b}	5.1E-03	3.0E-03	2.6E-03	2.2E-03	200
MAA ^b	2.8E-03	4.0E-03	5.0E-03	4.0E-03	200
MAG3 ^{a,b}	1.8E-02	1.4E-02	5.5E-03	5.2E-03	750
MDP ^b	6.1E-03	5.4E-03	2.7E-03	2.4E-03	750
MIBI (resting) ^{a,b}	1.5E-02	1.2E-02	8.4E-03	5.4E-03	1,100
RBC ^b - <i>in vivo</i> label	6.4E-03	4.3E-03	3.3E-03	2.7E-03	550
Sulfur colloid (IV)	1.8E-03	2.1E-03	3.2E-03	3.7E-03	300

^aRadiopharmaceuticals that do not cross the placenta significantly. They do deliver radiation exposure from their presence in the mother and are included for comparison.

^bDMSA = 2,3 dimercaptosuccinic acid

GHA = glucoheptonate

HDP = hydroxymethylene diphosphonate

HMPAO = hexamethylpropylene amine oxime

MDP = methylene diphosphonate

HSA = human serum albumin

MAA = macroaggregated albumin

MAG3 = benzoylmercaptoacetyl-triglycine

MIBI = methoxyisobutylisonitrile

RBC = red blood cells

rhodium (Rh, Z = 45), and palladium (Pd, Z = 46)] will be considered here. Description of the other members of the series (Z = 76 to 78) will be deferred until later in this Appendix.

Ruthenium is among the most abundant fission products in waste effluent from reprocessing of nuclear fuels (Nishimura *et al.*, 1988). Ruthenium has seven stable isotopes in the range ^{96}Ru to ^{104}Ru , with abundances ranging from 2 to 32 percent. Radioisotopes range from ^{93}Ru to ^{108}Ru ; many have half-lives less than 1 h, but three have half-lives greater than 1 d.

The only stable isotope of rhodium is ^{103}Rh . Five of the several radioisotopes and isomeres range from ^{97}Rh to ^{110}Rh . Among the several radioactive isotopes, ^{103}Ru and ^{106}Ru have half-lives and abundances that make them of interest for radiological protection. The daughter, ^{106}Rh , emits a high energy beta particle and is of importance in ruthenium dosimetry.

A.44.1 Biological Information

No data on ruthenium or rhenium content are given for ICRP Reference Man (ICRP, 1975). Studies on the absorption and metabolism of ruthenium were reviewed in ICRP Publication 30 and again summarized in Publication 56 (ICRP, 1980; 1989). The GI absorption fraction is accepted as 0.05. It is assumed that 15 percent of ruthenium entering blood is rapidly excreted, and the remainder becomes uniformly distributed. Biological retention halftimes are 8 d (35 percent), 35 d (30 percent), and 1,000 d (20 percent) for all tissues.

In absence of data, the absorption and biological behavior of rhodium was assumed by ICRP to be the same as described for ruthenium. A somewhat different behavior was accepted for palladium, which will be described separately.

A.44.2 Fetal/Placental Information

Early whole-body autoradiographic studies found that there was a marked deposition of ruthenium in the fetal membranes, as well as in maternal kidney and connective tissue (Nelson *et al.*, 1963). The concentration in the placenta was lower and seemed to follow blood clearance. It therefore seemed to be among the elements (actinides and some other heavy metals) that localized in the yolk sac.

This localization was confirmed in subsequent studies that measured the biokinetics of ^{106}Ru in rats (Nishimura *et al.*, 1988). Biological disposition varied with animal age and the chemical form in which the ruthenium was administered, but the percentage of the injected activity transferred across the placenta after intravenous

injection of $^{106}\text{RuCl}_3$ in rats consistently increased with gestational age. As an example, approximately 0.4 percent of the activity was transferred to the entire fetal mass at 20 dg. This is equivalent to an average concentration less than five percent of that in the dam. Markedly higher concentrations were found in the fetal membranes and quantitatively confirmed that the concentrations in the placenta and fetal membrane are higher than those in the fetus (Nishimura *et al.*, 1988).

Subsequent experiments by Levack *et al.* (1994a) found concentration ratios as high as 0.1 following administration to rats at various stages of gestation. Values of 0.2 were measured at 7 d after administration to near-term guinea pigs. Again in these studies, markedly elevated concentrations were detected in the yolk sac and placenta.

Studies of fetal-to-maternal concentration ratios with ^{106}Ru in rats were reviewed by Stather *et al.* (1987). Results have demonstrated that the fetal concentration, at term, is much lower than that of the mother, but the concentration ratio is larger when administrations are made in later stages in pregnancy. The results shown in Table A.7 illustrate these findings.

A.44.3 Radiation Dose Estimates

Stather *et al.* (1992) calculated the committed effective dose to the fetus from chronic ingestion of ^{106}Ru by the mother during the course of pregnancy. This value was $8.6 \times 10^{-10} \text{ Sv Bq}^{-1}$ when the concentration ratio in the fetus to that in the mother was 0.1 and the fraction assumed to be absorbed from the GI tract of the mother was 0.05. The ratio of the committed effective dose of the fetus to that of the mother was 0.08.

Table A.7—Uptake and concentration ratios of ruthenium in fetal and maternal tissues of rats (based on Stather *et al.*, 1987).

Time of Gestation	Percent Administered Activity in Dam at Birth	Percent Administered Activity in Fetus at Birth	Concentration Ratio of Fetus/Mother
1 week before conception	30.8	0.0025	0.0037
14 d	51.9	0.023	0.015
19 d	64.4	0.082	0.051

Sikov and Hui (1996) estimated radiation absorbed doses and dose rates for ^{106}Ru in equilibrium with ^{106}Rh introduced into the mother's blood at several stages of gestation and for different periods after intake. The cumulated doses through term following administration at three months of gestation or later was about 0.81 to 1.4 μGy per Bq injected.

A.45 Palladium

There are six stable isotopes of palladium (Pd , $Z = 46$); ^{102}Pd (0.96 percent), ^{104}Pd (11.0 percent), ^{105}Pd (22.2 percent), ^{106}Pd (27.3 percent), ^{108}Pd (26.7 percent), and ^{110}Pd (11.8 percent). Radioisotopes range from ^{98}Pd to ^{115}Pd and are listed in tables of isotopes; many have half-lives of less than 1 h, but ^{100}Pd , ^{101}Pd and ^{103}Pd have half-lives greater than 1 d.

A.45.1 Biological Information

No data on palladium content are given for Reference Man (ICRP, 1975). According to the ICRP (1981), the fractional absorption of palladium administered as chloride from the GI tract of rats is less than 0.005 and as oxide and sulfate is even smaller. A metabolic model for palladium is presented in ICRP Publication 30, Part 3 (ICRP, 1981).

Moore *et al.* (1975a) compared the retention and metabolism of ^{103}Pd as the chloride in male rats after intrathecal, oral, intravenous and inhalation administration. After oral administration, only about 0.4 percent of the initial activity was retained in the rats 3 d after administration. Extrapolation of the second component of the retention curve indicated that absorption from the GI tract was less than 0.5 percent of the initial activity. They found that retention of the ^{103}Pd in suckling rats was similar to that in adults; however, the amount absorbed and retained with time was significantly higher. The greatest amount of ^{103}Pd retained over time occurred after intravenous administration. Intrathecal administration resulted in somewhat less retention than IV administration and inhalation administration still less. Excretion after oral administration was almost all in the feces. With IV administration, ^{103}Pd was excreted approximately equally in the urine and feces. The highest concentrations of ^{103}Pd after IV administration, in decreasing order of amount, were in the spleen, kidney, liver, lung and

bone. After intrathecal administration the highest concentrations were in the lung, kidney, spleen, bone and liver.

A.45.2 Fetal/Placental Information

Pregnant rats (16 dg) were given ^{103}Pd intravenously; during the 24 h period after administration, they excreted 44.2 percent of the initial IV activity (Moore *et al.*, 1975b). The rats were killed 24 h after administration, the tissues were assayed, and concentrations were calculated for maternal and fetal tissues. The maternal kidney concentration was 160 times that in the blood, and maternal liver concentration was 87 times that in blood. The concentrations in ovaries, lungs and bone of the mother were about five to eight times that in blood. The placental concentration was 16 times that in maternal blood. The fetal liver concentration was about 0.4 of that in blood, and the average fetal concentration was about 0.2 of that in blood. The results indicated that palladium does not readily move across the placental barrier in the rat.

A.46 Silver

Silver (Ag, Z = 47) has two stable isotopes, ^{107}Ag and ^{109}Ag , with about equal abundances. It has about 20 radioisotopes, ^{102}Ag to ^{117}Ag , five of which have half-lives greater than 1 d.

A.46.1 Biological Information

Silver is a natural constituent of the human body, but has no known function. The silver content of the soft tissues of Reference Man is 790 μg (ICRP, 1975). The fractional absorption of silver from the GI tract is considered to be about 0.05. The metabolic model for silver allows for distribution of 50 percent from blood to liver and 50 percent to other tissues (ICRP, 1993). For all tissues, a 3.5 d half-life is assumed for 10 percent, 50 d for 80 percent, and 500 d for 10 percent.

A.46.2 Fetal/Placental Information

When ^{110m}Ag was fed to miniature pigs during the period from 50 dg through birth, the livers of the newborns had the highest concentrations. These were about twice those in maternal liver but, with nursing, had fallen to the same concentration by 3 d of age.

Comparative concentrations in other organs were similar to or less than in the sow although placental concentrations were about three times that of the maternal average (Gerber, 1993; Timmermans *et al.*, 1992).

A.47 Cadmium

Cadmium (Cd, Z = 48) has eight stable isotopes in the range ^{106}Cd to ^{116}Cd , five of which have abundances above 10 percent and several radioisotopes in the range of ^{103}Cd to ^{121}Cd . Many of the radioisotopes have half-lives of less than 1 h, but ^{109}Cd , $^{113\text{m}}\text{Cd}$, ^{115}Cd and $^{115\text{m}}\text{Cd}$ have half-lives greater than 1 d.

A.47.1 Biological Information

Cadmium is a natural but nonessential constituent of the human body. The cadmium content of Reference Man is 50 mg with soft tissues containing 38 mg (ICRP, 1975). The fractional absorption of dietary cadmium has been reported to be between 0.01 and 0.1, but the ICRP chose 0.05 as the fractional absorption of all inorganic compounds of cadmium from the GI tract (ICRP, 1980).

The ICRP indicated that the biological halftime for cadmium retention in the whole body is not less than 130 d and could be much greater (ICRP, 1980). Comparisons of excretion and total body burdens of cadmium in various groups of people indicate biological halftimes for cadmium retention in the whole body could be between 13 and 47 y. Studies have shown that stable cadmium concentrates primarily in the liver and kidney. The ICRP provides a metabolic model for cadmium in ICRP Publication 30 (ICRP, 1980).

A kinetic model of cadmium metabolism has been developed for the human (Kjellström and Nordberg, 1978). This model was found to be adequate for evaluating cadmium retention and distribution after inhalation by two types of people, one group exposed to cadmium through smoking and the other through work in a battery factory. Data from some conditions such as extremely high exposures did not fit the model well. The investigators concluded that the model is best applied for determining exposures required to reach a certain concentration in an organ.

A.47.2 Fetal/Placental Information

Using the radioactive isotope ^{115m}Cd , pregnant rats were studied to compare content in the fetus and placenta at different stages of pregnancy (Schulert *et al.*, 1969). Table A.8 shows the results, which illustrate the markedly elevated concentration in the placenta.

Christley and Webster (1983) demonstrated that in the mouse neither the yolk-sac placenta nor the chorioallantoic placenta protects the embryo from exposure to cadmium on day nine of gestation. The lowest level of cadmium administered (0.02 μg) could be compared to the estimated 1 to 2 μg cadmium contained in a single cigarette, of which 5 to 10 percent is assimilated during smoking. They considered that their data showed that no safe level of maternal exposure to cadmium exists below which the embryos would not be exposed.

Ahokas and Dilts (1979) orally administered cadmium to pregnant rats and found little cadmium transfer to the fetus after formation of the functional placenta. The placenta accumulated cadmium in increasing amounts with increasing gestational age. They felt that the differences in the results of their studies from others could possibly be explained by the fact that only two to three percent of ingested cadmium is absorbed and retained for transfer to the fetus. The large difference between placental and fetal cadmium accumulation may indicate that the cadmium in the placenta is protein bound and unable to cross to the fetus. The critical time of development when the embryo accumulates cadmium ingested by the dam appears to be between implantation and development of the functional placenta (day 10 to 11 of gestation) which is also the critical period of organogenesis.

Table A.8—Uptake of cadmium (^{115m}Cd) placenta and fetus after administration to pregnant rats. Results given as percent of injected activity (% IA) per organ or per gram (from Schulert *et al.*, 1969).

Day of Gestation	Fetus (% IA/organ)	Placenta (% IA/organ)	Fetus (% IA/g)	Placenta (% IA/g)
14	none detected	0.120	none detected	0.745
17	0.0121	0.512	0.0150	1.48
20	0.0509	0.596	0.0136	1.27

Pregnant rats were injected with ^{109}Cd and ^{65}Zn as chloride salts with radiochemical purity better than 99 percent (Lucis *et al.*, 1972). In the newborns ^{65}Zn was found in all tissues, but ^{109}Cd was detectable only in the liver, brain and intestinal tract. Placental tissue obtained on 19 dg showed that much more cadmium than zinc was accumulated in the placenta, but much less ^{109}Cd from the mother reached the fetuses than ^{65}Zn . Cadmium was found by Sonawane *et al.* (1975) to cross the rat placenta at three different levels of cadmium administration and at 12, 15 and 20 dg; however, higher percentages of cadmium accumulated in the fetus with increasing amounts of cadmium and increasing gestational age. The ratios of placental-to-fetal cadmium concentrations decreased with increasing amounts of cadmium administered.

After intravenous injection of cadmium into pregnant hamsters, Ferm *et al.* (1969) found detectable counts in embryonic tissue at 9 and 12 dg. Relative changes in the concentration of cadmium occurred in the uterus, placenta and embryo between 9 and 12 dg. On day 9, the average concentration of cadmium in the uterus to that in the maternal blood was 15 and on day 12, 7.9. On day 9, the average concentration in the placenta to that in the maternal blood was 12 and on day 12, 2.8. On day 9, the average concentration in the embryo to that in the maternal blood was 2.1 and on day 12, 0.033.

Kelman and Walter (1977) studied the passage of cadmium across the perfused guinea pig placenta and determined that the premise of a strong placental barrier against the movement of cadmium across the placenta may not be correct. The clearance of cadmium had a perfusion rate more than twice that of methyl mercury and larger than that of calcium measured under similar conditions. Cadmium clearance was linearly related to perfusion rate unlike methylmercury and calcium clearances. Their conclusion from their studies and the literature was that cadmium readily crosses the placenta but little cadmium accumulates in the fetus from an intravenous injection because most of the cadmium is sequestered in the liver and kidney of the mother. They warn that any pathological condition that might interfere with this mechanism could expose the developing fetus to greatly increased amounts of cadmium.

In another study, Kelman and Walter (1980) determined that the clearance of cadmium from dam to fetus was approximately six times greater than from fetus to dam. They also found that cadmium-related decreases in maternal blood flow to the placenta may account in part for teratological events observed when

cadmium is administered to the maternal system. This would severely hamper the exchange of gases across the placenta and fetal access to essential nutrients.

Studies in pregnant women compared cadmium levels in maternal blood, fetal cord blood, and placental tissues of smokers and nonsmokers (Kuhnert *et al.*, 1982). The percentage increase in cadmium as a result of smoking was 16 percent in the fetal cord blood, 32 percent in the placenta, and 59 percent in maternal blood. The increase in cadmium in the fetal cord blood was not significant. The ratio of cadmium in the maternal blood to that in the fetal cord blood was 1.6 in the smoker and 1.2 in the nonsmoker. The average cadmium level in the maternal blood was 2.2 ng g^{-1} of blood in the nonsmoker and 3.5 ng g^{-1} in the smoker. In the fetal cord blood the average was $1.9 \text{ ng cadmium g}^{-1}$ of blood in the nonsmoker and $2.2 \text{ ng cadmium g}^{-1}$ in the smoker. The placental content was $13.7 \text{ ng cadmium g}^{-1}$ in the nonsmoker and $18.1 \text{ ng cadmium g}^{-1}$ in the smoker.

Measurements of cadmium content in human placentas, maternal blood, and fetal blood, found that the concentrations were not significantly different among the tissues studied (Baglan *et al.*, 1974). However, they could not determine that the levels in blood were correlated with the level in the placenta.

According to a survey of pregnant women living in several areas of Belgium, the average content of cadmium in maternal blood was $1.5 \text{ ng cadmium g}^{-1}$ of blood while the average content of cadmium in the blood of the newborn was $1.0 \text{ ng cadmium g}^{-1}$ of blood (Lauwerys *et al.*, 1978). The authors concluded that the placenta plays a barrier role for the transfer of cadmium and is less permeable to cadmium than to other heavy metals such as lead and mercury.

Data on pregnant women living in other areas of Belgium were grouped as smokers and nonsmokers (Buchet *et al.*, 1978). Higher levels of cadmium were found in the blood of the smokers than in the blood of nonsmokers; however, the average levels in the blood of the newborns born to smoking mothers were slightly less than in the newborns born to nonsmokers. In another study of pregnant Belgium women (Roels *et al.*, 1978), the average cadmium content in the placenta was 15.7 ng g^{-1} of tissue in smokers and 12.5 ng g^{-1} in nonsmokers.

Zinc and cadmium levels were determined in 36 human embryos at ages from 31 to 78 dg, 14 second trimester fetuses, ranging from 85 to 185 d, and one 261 d old third trimester fetus. The mean concentration of cadmium in four intact embryos at 31 dg was below detectable limits, Chaube *et al.* (1973). The mean concentration in

the remaining 32 embryos (35 to 78 dg) was at most $0.07 \mu\text{g g}^{-1}$ wet tissue with little difference seen at the different ages. They analyzed the liver, brain and kidney of the fetuses from the second trimester but did not analyze the kidney in the third trimester fetus. The mean concentration in the liver during the second trimester was $0.114 \mu\text{g g}^{-1}$ and in the one fetus from the third trimester was $0.034 \mu\text{g g}^{-1}$. The mean cadmium concentration in the brain was $0.14 \mu\text{g g}^{-1}$ during the second trimester and below detectable limits in the third trimester. Kidney concentrations averaged $0.05 \mu\text{g g}^{-1}$. The investigators saw no trend related to age, sex or stage of development in these organs.

A study was carried out on a group of 40 women and their newborn offspring to determine cadmium levels in blood and urine of the mothers and the infants (Allesio *et al.*, 1984). These women were not occupationally exposed to cadmium. The cadmium levels in the blood of the women were significantly lower than those in a control group of 40 nonpregnant women of the same age range living in the same area. The investigators believed that this was the result of physiological hemodilution during pregnancy. The cadmium levels in the urine of both groups were identical, which suggests that the cadmium is not mobilized from tissue deposits during pregnancy. The cadmium levels in the blood and the urine of the infants were lower than those in the mother. The levels in the urine of the infants correlated well with those in the mothers' urine which probably indicates that the levels in the infants may depend on the amount of cadmium in the mother. The cadmium fraction that crosses the placental barrier is directly eliminated in the urine probably because no proteins are available to bind with the tissues.

Forty fetuses of 22 to 43 weeks gestation were analyzed for concentrations of several essential trace elements (Casey and Robinson, 1978). They found that only low levels of cadmium could be detected in samples of fetal tissues. Adult kidney and liver levels were much higher than the fetal range. Because concentrations in all fetal tissues were similar they concluded that no single organ would contribute more to the body burden than any other.

A.48 Indium

The only stable isotope of indium (In, Z = 49) is ^{113}In (4.2 percent); however, ^{115}In , which has a half-life of 6×10^5 y, occurs in nature with an abundance of 95.8 percent. There are more than 30 radioactive isotopes and isomeres ranging from ^{106}In to ^{124}In .

Many of these have half-lives of less than 1 h. Only ^{111}In (2.8 d) and $^{114\text{m}}\text{In}$ (50 d) have half-lives greater than 1 d.

Indium-111 is routinely used in nuclear medicine, and in the past $^{113\text{m}}\text{In}$ was used for some types of studies. $^{114\text{m}}\text{In}$ and its daughter product ^{114}In are found as contaminants in some preparations of ^{111}In .

A.48.1 Biological Information

The ICRP (1980) chose 0.02 as the fractional absorption of indium from the GI tract because studies with indium trichloride have shown this to be the approximate absorption in rats.

Toxicity studies (Castronovo and Wagner, 1971) have shown that toxicity of orally administered indium is much less than the toxicity of indium administered intravenously. These studies with ionic indium and hydrated indium oxide in mice showed that by 30 d after administration 87 percent of ionic indium had been excreted (35 percent in feces and 52 percent in urine). They found that 31 percent was eliminated with a biological halftime of 1.9 d and 69 percent with a biological halftime of 69 d. By 30 d after administration 63 percent of the hydrated indium oxide had been excreted (53 percent in the feces and 10 percent in urine). Eighteen percent was eliminated with a biological halftime of 2 d and 82 percent with a biological halftime of 73.8 d.

In the ionic form, the highest concentrations of indium are found in red marrow, kidney, liver and spleen (ICRP, 1980; 1987). The metabolic model for indium assumes that indium is retained in all organs and tissues with halftimes of 2 d (30 percent) and 70 d (70 percent). Other considerations pertain for the several compounds prepared for medical uses (ICRP, 1987).

A.48.2 Fetal/Placental Information

Studies in pregnant animals have been performed with the indium radioisotopes that are used for clinical evaluations of the placenta. Mahon *et al.* (1973) administered indium with and without carrier in pregnant rabbits. Without carrier, the concentration of $^{113\text{m}}\text{In}$ activity in the placenta at 1 h after administration was 853 times that in the fetus and 3.8 times that in the blood. With carrier the ratio of placenta to fetus for $^{114\text{m}}\text{In}$ was 59 and to blood was 1.6. Studies with colloidal indium with lutetium carrier showed similar patterns.

Wochner *et al.* (1970) found that carrier-free ^{113m}In binds specifically to transferrin after intravenous injection. According to these authors, in the nonpregnant state transferrin binding of carrier-free indium is so complete that it may be used for plasma volume determinations. Radioactive indium reaching the placenta is released from transferrin, does not cross into the fetal circulation, but accumulates in the placenta. This has been confirmed by studies by Gruber *et al.* (1970) who found that virtually no indium crossed to the fetus of rats but large amounts accumulated in the placenta. The presence of very small amounts of carrier indium ($10 \mu\text{g kg}^{-1}$) significantly lowers the placental concentration of indium without much change in the blood levels or fetal concentration (Mahon *et al.*, 1973).

Pregnant and nonpregnant mice were studied for localization and retention of radioindium (Lathrop *et al.*, 1992). A limited study was also performed in guinea pigs and a monkey. Linear compartmental models with associated rate constants were constructed and fitted to the data points for nonpregnant and pregnant animals. Transfer of indium to the intestine was found to be two directional and no fecal excretion occurred.

Niehoff *et al.* (1970) found that 2.5 percent of ^{113m}In administered to a pregnant dog at term was in the placenta. Virtually no activity was found in the amniotic fluid or the whelps at 45 min after administration.

Indium-111 is routinely used in nuclear medicine, and in the past ^{113m}In was also used. Indium-114m with its daughter product ^{114}In are found as contaminants in some preparations of ^{111}In . Indium radioisotopes have been used to label blood elements such as lymphocytes and platelets for nuclear medicine procedures. However, no studies have been reported with these agents in pregnant women.

A.48.3 Radiation Dose Estimates

Niehoff *et al.* (1970) used their data from a pregnant dog to estimate a range of dose factors for the human fetus that ranged from 0.81 to 9.7 $\mu\text{Gy MBq}^{-1}$ when ^{113m}In was administered intraveneously.

Sastry *et al.* (1976) calculated radiation doses for radionuclides used in placentography including ^{113m}In chloride. They reported that at 30 weeks of pregnancy in the human, 0.8 percent of administered activity crosses the placenta and has an effective halftime equal to the physical half-life of ^{113m}In . They estimated,

apparently on the basis of blood volume, that the placental content of ^{113m}In would be 4.8 percent of the administered activity and the uterine wall content would be 1.8 percent. They estimated the dose from ^{113m}In to the fetal whole body at the 30th week of pregnancy to be $4.6 \mu\text{Gy MBq}^{-1}$. This is within the range given by Niehoff *et al.* (1970).

A.49 Tin

The 10 stable isotopes of tin (Sn, Z = 50) range from ^{112}Sn to ^{124}Sn ; ^{116}Sn (14.2 percent), ^{118}Sn (24.0 percent), and ^{120}Sn (33.0 percent) are the most abundant and there are more than 20 radioisotopes and isomeres ranging from ^{108}Sn to ^{132}Sn . Many of these have half-lives of less than 1 h, but five radioisotopes have half-lives greater than 15 d.

A.49.1 Biological Information

Tin is a natural constituent of the human body. The tin content of Reference Man is 5.8 mg in soft tissues, with less than 12 mg in the skeleton (ICRP, 1975). The fractional absorption of dietary or inorganic tin from the GI tract is typically about 0.02, which has been adopted as the f_1 value (ICRP, 1981).

As described in ICRP Publication 30 (ICRP, 1981), the ICRP metabolic model from animal studies have shown that several compounds of tin are concentrated to a larger degree in skeleton than in other organs (ICRP, 1981).

A.49.2 Fetal/Placental Information

MacDonald *et al.* (1970) studied ^{113}Sn injected into pregnant rabbits as the contaminant in ^{113m}In . At 2 d post-injection, 33 to 52 percent of the ^{113}Sn was recovered in the maternal body but less than four percent was in the liver, spleen, GI tract, and kidneys. After 2 d, 23 percent was in these organs. Between one percent to three percent of the administered ^{113}Sn was in the fetuses at 1 d postinjection. This decreased to 0.1 percent to 0.5 percent at the time of normal delivery, 7 to 11 d after injection. The burden of tin in the offspring decreased more rapidly than the maternal burdens.

A.50 Antimony

Antimony (Sb, Z = 51) is a brittle metal found in many minerals and commercial products such as paints and ceramics. Antimony and its compounds are toxic. It has two stable isotopes, ^{121}Sb and ^{123}Sb and at least 27 unstable isotopes have been identified. Most have very short half-lives while ^{125}Sb has the longest half-life of 2.7 y.

A.50.1 Biological Information

The antimony content of the body is approximately 7.9 mg with a dietary intake of 34 μg (ICRP, 1975). The fractional absorption from the GI tract has wide variability but is taken to be 0.1 if ingested in diet (ICRP, 1995).

Antimony partition among tissues is species dependent. Human distribution studies suggest that antimony is concentrated to some degree by the liver, kidneys and skeleton. ICRP Publication 69 (ICRP, 1995) considers that 20 percent of antimony leaving the transfer compartment goes directly to excretion, 40 percent to mineral bone, 5 percent to liver, and the remaining 35 percent is uniformly distributed throughout all other organs and tissues. For all organs and tissues, biological retention halftimes are 5 d (85 percent), 100 d (10 percent), and 500 d (5 percent).

A.50.2 Fetal/Placental Information

Gerber *et al.* (1982) intraperitoneally injected rats with ^{125}Sb at 12 dg and sacrificed them at times beginning 2 h afterwards. Concentrations in the fetuses were substantially less than in the placentas at early times but were only slightly less than the average maternal tissue. Placental concentrations remained about twice the maternal average but fetal concentrations decreased during the 7 d period.

Fetal to maternal concentrations of 0.8 to 0.06 were calculated from these data (Roedler, 1987).

A.51 Tellurium

Tellurium (Te, Z = 52) is a p-type semiconductor that is found most often as a telluride of gold. Twenty-one isotopes have been identified ranging from ^{115}Te to ^{135}Te . Natural tellurium consists of

eight stable isotopes in the range ^{120}Te to ^{130}Te , and one radioactive isotope, ^{123}Te , that has a half-life of 1.2×10^{13} y. More than 20 unstable isotopes and isomers have been identified in the range of ^{106}Te to ^{138}Te . ^{132}Te is of particular interest relative to its release in accidents involving nuclear detonations.

A.51.1 *Biological Information*

Based on the literature concerning the biological behavior of tellurium reviewed in ICRP Publication 67 (ICRP, 1993), a value of 0.3 was assigned as the GI absorption factor. The model assumes that 50 percent of the tellurium that enters blood will be promptly excreted and that 25 percent is distributed to skeleton, which is assigned a 10,000 d retention halftime. A 20 d retention halftime is used for soft tissues, being distributed as 2.3 percent to kidney, 0.2 percent to thyroid, and 22.5 percent to remaining tissues.

A.51.2 *Fetal/Placental Information*

Tellurium-127 as the acid was intraperitoneally injected in rats and assayed in maternal and fetal tissues beginning at 4 h afterwards (Agnew and Cheng, 1971; Agnew *et al.*, 1968). Most of the tellurium in fetal tissue was bound to protein and initial concentrations in fetal liver and kidney were only a small fraction of those in the corresponding maternal organs. Relative fetal concentrations increased during the week of study; the kidney ratio remained low but the concentration in fetal liver approximated that of the dam. Autoradiographic studies with the $^{123\text{m}}\text{Te}$ isotope indicated that placental concentrations were similar to or higher than maternal blood (Agnew, 1972). The studies confirmed that the fetal concentrations were substantially lower than these tissues and that the highest fetoplacental concentrations were in placenta and yolk sac, followed by fetal liver, and lower concentrations in other tissues.

A.52 **Iodine**

Iodine (I, Z = 53) is a highly reactive halogen that volatilizes at ordinary temperatures. There is one stable isotope, ^{127}I , and 23 known radioisotopes. Several radioisotopes are common products of nuclear fission and have been released to the environment by nuclear detonations and reactor accidents.

Radioiodines are also commonly used in diagnostic nuclear medicine and some, especially ^{131}I with an 8 d half-life, are used in medical facilities in gigabecquerel amounts for the treatment of thyroid disorders and cancer.

A.52.1 *Biological Information*

Iodine is an essential element that is required for normal thyroid function. The iodine is concentrated by the thyroid gland and incorporated into the three thyroid hormones, diiodothyronine (T₂), triiodothyronine (T₃), and thyroxine (T₄). Thyroxine is necessary to maintain a normal metabolic state in all tissues of the body. Of that ingested or inhaled essentially all reaches the transfer compartment as absorption is rapid and complete with an f_1 value of 1.0 (ICRP, 1989). Medical conditions markedly affect thyroid functions, but a normal thyroid gland cumulates between 8 and 30 percent of that ingested or inhaled as inorganic iodide.

The ICRP models for adults assume a 30 percent uptake by the thyroid gland and the remaining 70 percent is assumed to go directly to excretion. Of that taken up by the thyroid, an "apparent" biological half-life of 90 d has been assumed. From the thyroid, the iodine is assumed to be uniformly distributed as organic compounds throughout all organs and tissues of the body. The organic iodine compounds leave tissue with a biological halftime of 12 d; one-tenth of this goes directly to fecal excretion and the rest is returned to the transfer compartment as inorganic iodine (ICRP, 1987; 1989).

A.52.2 *Fetal/Placental Information*

Several studies have been performed to measure uptake of iodide in the fetal thyroid but iodine kinetics in the fetus are not well understood. Beierwaltes *et al.* (1963) and Evans *et al.* (1967) found that although the amounts of radioactivity in the fetal thyroids were highest at term, the concentrations were highest during the five to six month period of the pregnancy. Dyer and Brill (1972) and Aboul-Khair *et al.* (1966) also found similar trends in uptake values; however, neither reported values for stages beyond the sixth month. Hodges *et al.* (1955) measured the uptake of ^{131}I in the thyroid of nine fetuses that were aborted for therapeutic reasons. Book and Goldman (1975) reviewed human and animal studies and concluded that the ratio of the fetal thyroid concentration

to the maternal thyroid concentration is about 1.2 at three months, 1.8 during the second trimester, and 7.5 in the third trimester.

Aboul-Khair *et al.* (1966) attempted to determine the biological halftimes of iodide in the fetal thyroid. Although their data were limited, they felt that the results showed the fetal thyroid gland metabolizes iodine in a very different way from that of the adult gland. Over the fetal age group studied, they estimated a maximum biological halftime in the fetal thyroid of 28 h. Stieve *et al.* (1985) stated that the uptake of iodine in the mother during pregnancy is higher than normal values, that the biological halftime of iodine in the mother's thyroid is between 80 and 120 d, and that the biological halftime in the fetus is about 4 to 13 d. Johnson (1982) estimated the halftime of iodine in the fetal thyroid to be very long at 90 d of fetal age, soon after the fetal thyroid has started to concentrate and metabolize iodine. He stated that the retention halftime decreases to about 1,300 d, 120 d, and 70 d at 100, 200 and 270 d of age, respectively.

Roedler (1987) questioned these long halftimes on the basis of the data from Aboul-Khair *et al.* (1966) together with the consideration that the halftime of iodine in the adult thyroid may be as long as 120 d while the halftime in the newborn is only about 15 d. Roedler recommended a biological halftime value of 15 h for weeks 13 to 15, 61 h for weeks 15 to 19, and a linear increase to 15 d at term. Johnson (1987), however, has stated that the data of Aboul-Khair *et al.* (1966) can only be used to estimate the combination of uptake fraction and halftime of iodine in the fetal thyroid but not the halftime alone. According to Johnson's model, the short halftimes proposed by Roedler would result in too large an organic pool. Variations in the selected retention times in the fetal thyroid result in large differences among the estimates of radiation absorbed doses received by the fetal thyroid.

Several models have been proposed for calculating the radiation absorbed dose to the fetal thyroid from radioisotopes of iodine taken in by the mother in the form of sodium iodide (Aboul-Khair, 1966; Dyer and Brill, 1969; Johnson, 1982; 1987; Roedler, 1987). Prior to the time that the fetal thyroid begins to concentrate iodine, at about 11 weeks after conception, the thyroidal dose is not considered to be of special consideration. The most comprehensive biokinetic model for iodide in the pregnant woman was developed by Johnson (1982). Zanzonico and Becker (1992) modified Johnson's model to include slow exchange of organic iodine between the maternal and fetal circulations and calculated fetal absorbed doses

for mothers suffering from hyperthyroidism. They also determined the effect of thyroid blocking on the fetal thyroid dose.

Watson (1992c) has also modified Johnson's model slightly and used the SAAM (simulation, analysis and modeling) software to calculate transfer rate constants and residence times for iodide in the pregnant woman with normal thyroid. The S values for the fetal thyroid were derived from a mathematical model described by Johnson (1982). Although the dose estimates (Table A.9) calculated from Watson's model are somewhat smaller than those of Johnson, they are generally larger than those of Roedler (1987).

Other estimates of radiation dose to the fetal thyroid from several iodine radioisotopes are given by Sikov and Hui (1996). They also calculated values of dose to the whole embryo/fetus from these radionuclides. Dose estimates for selected iodinated radiopharmaceuticals are presented in Russell *et al.* (1997b).

A.53 Xenon

Xenon (Xe, Z = 54) is a noble or inert gas with a density greater than that of air. Natural xenon is composed of nine stable isotopes and 22 radioactive isotopes and isomers have been identified. Of these, ^{133}Xe and ^{135}Xe are produced in large quantities by neutron irradiation of air in air-cooled nuclear reactors. The ^{133}Xe is commonly used in nuclear medicine diagnostic studies to image lungs after inhalation or cerebral blood flow after injection.

Table A.9—Estimated absorbed doses in fetal thyroid from radioiodine isotopes administered to the pregnant woman (from Watson, 1992c) (mGy MBq⁻¹).

Gestational Age (month)	^{123}I	^{124}I	^{125}I	^{131}I
3	2.7	24	290	230
4	2.6	27	240	260
5	6.4	76	280	580
6	6.4	100	210	550
7	4.1	96	160	390
8	4.0	110	150	350
9	2.9	99	120	270

A.53.1 Biological Information

No metabolic model was proposed by ICRP Publication 30 "since dose equivalent rates from gas absorbed in tissue or contained in the lungs will be negligible in comparison with the dose equivalent rates to tissues from external irradiation" (ICRP, 1981).

The biological behavior and dosimetry of xenon isotopes as used in nuclear medicine are described in a MIRD report by Atkins *et al.* (1980). This forms the basis for the model in ICRP (1987), which also presents tables of radiation doses.

The MIRD committee developed biological parameters for the distribution of xenon, an inert gas used for ventilation studies in humans (Atkins *et al.*, 1980). At the end of 5 min of breathing xenon and air from a spirometer, the concentration of radioxenon in the lungs is approximately the same as that in the spirometer. Equilibrium concentration would require up to 30 h of rebreathing (Susskind *et al.*, 1977). Noble gases are more soluble in lipids than in water; hence, tissues with high fat content concentrate more of the gas than do other tissues. In MIRD Dose Estimate Report No. 9 (Atkins *et al.*, 1980), the compartment with the slowest turnover rate constant was assumed to represent fatty tissues. The halftime for washout from this compartment, as measured by Susskind *et al.* (1977), averaged 10.5 h and ranged from 7.59 to 17.04 h. The person with a halftime of 7.59 h had 24.2 percent body fat while the person with a halftime of 17.04 h had 63.5 percent body fat.

A.53.2 Fetal/Placental Information

The primary component of the radiation dose to the fetus from the immersion of the pregnant woman in a cloud of xenon could be assumed to be equal to the adult dose for each specific radioisotope. Given the concentration values of the air immersion, the dose could be calculated from tabulated ALI values for the specific isotope of interest.

A model for the behavior of noble gases and estimates of radiation absorbed dose from ^{133}Xe in the embryo/fetus are given in Sikov and Hui (1996).

A.54 Cesium

Cesium (Cs, Z = 55) is an alkali metal with a single stable isotope, ^{133}Cs . In addition, there are 20 unstable isotopes and isomers with widely varying half-lives. The radioisotopes of primary

concern are ^{134}Cs and ^{137}Cs . Radiocesium is among the most abundant fission products and so is an important fallout contaminant following nuclear detonations or reactor accidents.

Radiocesium readily enters the food chain through grazing livestock, concentrating in the meat of animals. It is also secreted in milk. The beta-gamma emitting isotope, ^{137}Cs , with a 30.2 y half-life is used widely in medical and commercial facilities to provide long-lived radioactive sources and is used in gigabecquerel quantities for brachytherapy sources to treat cancer.

A.54.1 Biological Information

Metabolically, cesium is an intercellular electrolyte, which resembles potassium, and is uniformly distributed throughout all organs and tissues of the body. Absorption from the GI tract is complete and rapid with a fractional transfer value of one.

The retention of cesium can be described by a two exponential expression. Of the cesium entering the transfer compartment, 10 percent is translocated to a tissue compartment with a retention halftime of 2 d and 90 percent to a compartment with a retention halftime of 110 d (ICRP, 1989). It is often assumed that an overall retention value of 84 can be used for normal adult women.

A.54.2 Fetal/Placental Information

There is fair agreement about the interspecies content of radio cesium although there are differences related to time after administration and stage of gestation. There appears to be little or no placental discrimination for ^{137}Cs relative to potassium. Some workers, such as Nelson *et al.* (1961) found elevated concentrations of ^{137}Cs in developing cartilage of fetal mice. Kaul *et al.* (1966) reported that the specific activity of ^{137}Cs relative to potassium in bone and soft tissues of adults was not significantly different from the activities found in fetuses. They found also that the muscular tissue in the mother, fetus and placenta were comparable (Kaul *et al.*, 1966). The bone to muscle tissue ratio has been analyzed in human samples collected during periods of fallout in the 1960s; reported values ranged from 1:2 to 1:15.

Wilson and Spiers (1967), among others, studied cesium distribution in humans and found the concentration in the fetus to be similar to that in the mother. However, there is agreement that biological halftimes are shorter during pregnancy than in the non-pregnant woman (Bengtsson *et al.*, 1964; Bertelli *et al.*, 1992;

Rundo and Turner, 1992; Zundel *et al.*, 1969). The most comprehensive measurements of the halftimes in pregnant women were made by Zundel *et al.* (1969) who studied 24 women during their pregnancy. These investigators found in six women studied during and immediately after their pregnancy that the mean halftime of cesium was 47 d during pregnancy and 71 d after the pregnancy ended.

Sikov and Hui (1996) used a biokinetic model to calculate estimates of absorbed doses and dose rates for the fetus from ^{134}Cs and ^{137}Cs . They assumed a biological halftime of 84 d in the period of zero to five months, 70 d for five to six months, and 50 d for seven to nine months.

The alternative approach, using residence times for ^{134}Cs and ^{137}Cs in the pregnant woman, was calculated as an illustration specifically for this Report by using 47 d as the biological half-time of cesium in pregnant women. Absorbed dose estimates for the fetus through the first five months of pregnancy have been calculated (Table A.10) by using S values from a mathematical model describing the nongravid uterus for early pregnancy (C[h]risty and Eckerman, 1987) and from a mathematical model describing the uterus and fetus at the end of the first trimester for the period from three through five months (Davis *et al.*, 1987). These estimates are somewhat less than those calculated by Sikov and Hui (1996).

A chronic maternal exposure to ^{137}Cs would result in a uniform fetal distribution equal to the maternal soft tissue distribution. Assuming the source of the exposure is removed, the fetal biological halftime would be 49 d, the same as in the pregnant woman. If the source of exposure is not removed, as for example, in contaminated meat products, the continued intake must be considered.

A.55 Barium

Barium (Ba, Z = 56) is a member of the alkaline earth group that chemically resembles calcium. Naturally occurring barium is a mixture of seven stable isotopes with thirteen radioactive isotopes,

Table A.10—*Estimated absorbed doses for the fetus from an intake of radiocesium by the mother (mGy MBq⁻¹).*

Stage of Pregnancy	^{134}Cs	^{137}Cs
0 through 2 months	14	5.6
3 through 5 months	11	4.3

most with relatively short half-lives. The longer lived radioisotopes include ^{131}Ba and ^{140}Ba with half-lives of about 12 d and ^{133}Ba with a half-life of over 10 y.

A.55.1 *Biological Information*

The GI tract discriminates against barium relative to calcium or strontium and barium is less well absorbed and eliminated more rapidly (Leggett, 1992a). ICRP assigned the f_1 value of 0.1 in Publication 30 (ICRP, 1979) but a value of 0.2 was adopted in Publication 67 (ICRP, 1993). That report reviews the literature and presents a detailed description of the metabolic model for the alkaline earth elements, including specific coefficients for barium.

A.55.2 *Fetal/Placental Information*

Little information is available about the placental transfer of barium. In a study carried out by Wilkinson and Hoecker (1953), four rats were injected with $^{140}\text{Ba}(\text{NO}_3)_2$ at 15 d gestation and killed 5 d later. The total average litter content of barium was 9.88 percent of the injected dose with 0.31 percent contained in the placentas. The average individual content was 0.84 percent per fetus and 0.03 percent per placenta.

Comparisons of ^{140}Ba and ^{45}Ca in near term rats after simultaneous intravenous administration of the chloride at different stages of gestation indicated that the Ba/Ca ratio was about 0.4 (Taylor and Bligh, 1992). The transfer of barium (0.018 percent maternal dose/newborn) was about 15 percent of that found for calcium (0.128), but an overall transfer ratio of Ba:Ca was suggested.

Incubating embryonic chick bones *in vitro* showed that ^{140}Ba was discriminated against in favor of ^{45}Ca and that this was a function of viable bone cells (Moore, 1964). A maternal intake of barium would result in a fraction being distributed in fetal tissue. A small component of this would be deposited in fetal bone with an effective half-life equal to the physical half-life of the barium radioisotope.

A.56 Lanthanide Series - General

The group of 15 elements that are located in Group III is often called the lanthanide series after its initial element, lanthanum (Table A.11). These elements which are found in certain rare earths, display similar, but not identical, chemical behaviors, being

Table A.11—*Lanthanide series elements.*

Atomic Number (Z)	Symbol	Name
57	La	Lanthanum
58	Ce	Cerium
59	Pr	Praseodymium
60	Nd	Neodymium
61	Pm	Promethium
62	Sm	Samarium
63	Eu	Europium
64	Gd	Gadolinium
65	Tb	Terbium
66	Dy	Dysprosium
67	Ho	Holmium
68	Er	Erbium
69	Tm	Thulium
70	Yt	Ytterbium
71	Lu	Lutetium

influenced by the prevalent valence states. As described in ICRP Publication 30 (ICRP, 1981), their biological dispositions, including GI absorption, mostly show similarities, especially in relationship to considerations of interest to radiological protection, although some differ markedly.

Only cerium, which has especially important radioisotopes and serves as the prototype for the series, and gadolinium, which is used as a contrast agent for MRI, have been investigated during pregnancy. Accordingly, information about other members of the series will only be listed in a table and considered in summary. It is noted, however, that all of these elements have a large number of radioactive isotopes and except for promethium, all have stable isotopes.

A.56.1 *Biological Information*

The revised fractional absorption value from the GI tract that was assigned to cerium (0.005) in ICRP Publication 67 (ICRP, 1993) may be considered to apply to all of the lanthanides, and is in accord with the values tabulated in Publication 68 (ICRP, 1994).

As a rough approximation, the principal organ of deposition can be considered to be the liver. Of lanthanides that leave the transfer compartment, about 50 percent would be deposited in liver, 30 percent in mineral bone, and the remaining 20 percent would be

distributed throughout all other organs and tissues. Excretion is very slow with the biological half-life likely to be over 3,500 d (ICRP, 1991b).

A.56.2 Fetal/Placental Information

No information concerning the biological behavior of the lanthanides during pregnancy was located except for cerium and gadolinium, described in the following sections. However, they can be assumed to behave in a similar manner to cerium.

A.57 Cerium

Cerium (Ce, Z = 58) is the most thoroughly studied rare earth in the lanthanide series, and serves as the prototypic element for describing the metabolism and evaluating the dosimetry of this series. It is an iron-gray lustrous metal that is used extensively in the manufacture of pyrophoric alloys. There are over 20 isotopes of cerium, four making up naturally occurring cerium. Of importance are ^{141}Ce (half-life = 32 d) and ^{144}Ce (half-life = 285 d); both are beta emitting radioisotopes that are produced by neutron activation of stable cerium. These radionuclides may be found as contaminants in nuclear plants and in fallout from nuclear detonations.

A.57.1 Biological Information

The ICRP assigned a transfer fraction of 0.0003 for all compounds of cerium (ICRP, 1979); this was subsequently revised to 0.001 (ICRP, 1989), and more recently to 0.0005. The fractional absorption of cerium was studied in an accidental inhalation by a person and was found to be very small.

The ICRP model assumes that of the cerium entering the transfer compartment, 50 percent is deposited in liver, 30 percent in skeleton, and 20 percent in all other tissues. The retention halftime in all tissues is taken to be 3,500 d (ICRP, 1989).

A.57.2 Fetal/Placental Information

Cerium concentrates in the chorioallantoic placenta and yolk sac of rats at a concentration that is one or two orders of magnitude greater than the fetus (Zylicz *et al.*, 1975b). When cerium chloride was injected into the circulation of pregnant rats that were

sacrificed 24 h later, the concentration in various structures was independent of gestational age, comparing 15 d to 19 d fetuses (Mahlum and Sikov, 1968). Twenty-two percent of the total cerium content of 20 d fetuses was in the liver and 47 percent in the skeleton. The remaining 30 percent was distributed in the soft tissues. In contrast, in the adult rat at 1 h after injection, 75 percent of the cerium content of the body is in the liver, 13 percent in the skeleton, 2 percent in the kidneys, and the remaining 10 percent distributed throughout the remaining soft tissues.

Cerium-144 was injected as citrate in pregnant mice that delivered normally 48 to 72 h after injection (Naharin *et al.*, 1969). On the day after injection, 55 percent of the body burden was in the liver and 33 percent in the bone, but after 220 d, 3 percent was in the liver, and 95 percent in bone. The fetal uptake was 2.3 percent of the mother's body burden per individual pup. When delivered by Caesarian section 24 h after injection, however, each fetus contained only 0.06 percent. It was not clear if the difference was due to placental transfer or to external contamination.

When the newborn mice were allowed to nurse, the body burden increased until 11 d and then decreased exhibiting a two phase excretion pattern that was slightly shorter than that of adults (Naharin *et al.*, 1969). The total body burden of the litters fell as the time between mating and administration of the isotope increased. Thus it appeared that the amount of cerium available to the fetuses, *i.e.*, circulating in the maternal blood, determines the fetal uptake. Once fixed in the maternal skeleton, very little is transported to the fetus.

It is concluded that an acute maternal intake would result in a small fraction being transported to the fetus. Approximately 50 percent of the fetal content would be distributed in the soft tissue and 50 percent in the bone which with time would shift to nearly 100 percent in the bone. The fraction transported to the fetal tissue would progressively lessen as the time between the intake and pregnancy increased.

Zylicz *et al.* (1975b) studied the effect of calcium chelate on the ¹⁴⁴Ce retention in pregnant rats. Rats exposed at 17 and 21 dg contained 90 percent of the injected dose at 24 h. After administration of calcium chelate this was reduced by 26 percent. Rats contaminated at 19 dg contained almost 100 percent of the dose at 24 h which was reduced by 13 percent after administration of the chelate. Based upon this study, cerium could be effectively removed from maternal and fetal tissue if a calcium chelate is immediately given.

Sikov and Hui (1996) calculated that the cumulated radiation doses to the embryo/fetus from maternal injection of 37 kBq ^{144}Ce at various times during the fetal period would be in the range of 3 to 10 μGy . Slightly greater doses are associated with administration of ^{141}Ce .

A.58 Gadolinium

Gadolinium (Gd, Z = 64) is a rare-earth lanthanide and has the highest thermal neutron capture cross-section of any element. Natural gadolinium has seven stable isotopes; in addition there are 10 unstable isotopes with widely varying half-lives. Because of its high magnetic moment and low toxicity, gadolinium is commonly used as a contrast medium for diagnostic magnetic resonance imaging studies.

A.58.1 *Biological Information*

The fractional absorption of gadolinium is considered in ICRP Publication 67 to be 0.0005 for all compounds (ICRP, 1993). Based on the model for cerium, it is assumed that 50 percent is translocated to the liver, 30 percent to the mineral bone, and 20 percent to the other tissues. Of that deposited, the biological half-life is assumed to be 3,500 d.

A.58.2 *Fetal/Placental Information*

Compounds and chelates of gadolinium are used as contrast agents in magnetic resonance imaging under a variety of formulations and trade names. A review of the safety of one representative agent, Magnevist®, indicates that it "has been shown to cross the placenta and appear within the fetal bladder only moments after intravenous administration" (Shellock and Kanal, 1994). The authors assumed that related contrast agents would have a similar behavior and that they would be excreted into amniotic fluid, swallowed, and again filtered and excreted.

A.59 Hafnium

Hafnium (Hf, Z = 72) is a rare earth metal with a high absorption cross section for thermal neutrons, and so is used for nuclear

reactor control rods in submarines. Natural hafnium consists of six isotopes, five of which are stable. The sixth, ^{174}Hf , is an alpha-ray emitter with a half-life of 2×10^{15} y. There are 14 other radioactive isotopes, with half-lives extending to 1×10^6 y.

Because of its chemical similarity to zirconium, hafnium is assumed to have similar biological behavior. The fractional absorption of hafnium is assumed to be 0.002 for all compounds (ICRP, 1980). Of that leaving the transfer compartment, 50 percent is assumed to be translocated to mineral bone and retained with a biological half-life of 8,000 d. The other 50 percent is considered to be uniformly distributed to all other organs and tissues of the body and the biological half-life is assumed to be 7 d. Hafnium is assumed to be uniformly distributed over the bone surfaces (ICRP, 1980).

Hafnium differs from many of the other rare earth metals in that a greater fraction is deposited in organs and tissues other than the mineral bone. There is no direct information on the placental transfer of hafnium or its behavior in the embryo/fetus.

A.60 Tantalum

The metal tantalum (Ta, Z = 73) is used widely to make high-melting point alloys with good strength and hardness. Natural tantalum consists of two isotopes: ^{181}Ta is stable with an abundance of more than 99.9 percent and ^{180}Ta which is radioactive with a half-life of 10^{13} y. Seventeen other radioisotopes are known to exist; of those, ^{179}Ta has a half-life of 665 y and ^{182}Ta a half-life of 115 d. The remaining isotopes are relatively short lived.

The fractional absorption of tantalum is assumed to be 0.001 for all compounds (ICRP, 1980). Of tantalum leaving the transfer compartment, 30 percent is considered to be translocated to mineral bone and retained with a biological half-life of 100 d. Another six percent goes to the kidneys, while the remainder is assumed to be uniformly distributed throughout all other organs and tissues; equal fractions are assumed to be retained with biological half-lives of 4 and 100 d.

No information was located relative to deposition during pregnancy. It is not known whether tissue of the embryo/fetus participates in the 64 percent that is distributed through organs and tissues other than mineral bone and kidneys.

A.61 Tungsten

Tungsten (W, Z = 74) is a metal with a wide variety of uses ranging from filaments in electric lamps to targets for x-ray tubes, and to many high temperature uses. Natural tungsten consists of five stable isotopes. Seventeen radioactive isotopes are known, with half-lives up to 140 d.

The fractional absorption of tungsten is assumed to be 0.01 for tungstic acid and 0.3 for all other compounds (ICRP, 1980; 1994). Most of the tungsten leaving the transfer compartment, 95 percent, is assumed to go directly to excretion. Another 2.5 percent is translocated to mineral bone, and 2.5 percent to liver, kidneys and spleen. Of the material deposited in the mineral bone, biological retention halftimes are assumed to be 5 d (20 percent), 100 d (10 percent) and 1,000 d (70 percent). For tungsten deposited in any other organ or tissue, biological retention halftimes are assumed to be 5 d (70 percent) and 100 d (30 percent).

No fetal or placental information was located.

A.62 Rhenium

Rhenium (Re, Z = 75) is a dense metal that is used to produce alloys. Natural rhenium consists of one stable isotope, ^{185}Re , and one radioisotope, ^{187}Re , that has a half-life of 7×10^{10} y. Nineteen additional radioisotopes are known; the longest half-life, 169 d, is that of $^{184\text{m}}\text{Re}$.

A.62.1 Biological Information

The metabolism of rhenium appears to be similar to technetium. The fractional absorption of rhenium is assumed to be 0.8 for all compounds. Except for the thyroid, stomach wall and liver, rhenium is assumed to be uniformly distributed throughout all organs and tissues of the body (ICRP, 1980).

A.62.2 Fetal/Placental Information

No reports on placental or fetal deposition were located. It might be assumed that some compounds of rhenium would be transferred to the embryo/fetal tissue with patterns resembling those of the technetium analogs.

A.63 Platinum Series

Osmium (Os, Z = 76), iridium and platinum are the Group VIII elements of the sixth period that complete the platinum series. As was discussed for platinum elements of the fifth period, ruthenium, rhodium and palladium (Z = 44 to 46), these three elements share commonalities and display similar chemical and biological behaviors. Osmium has six isotopes in the range ^{184}Os to ^{192}Os that are stable or have stable isomeres. There are over 20 radioactive isotopes, including long-lived ^{186}Os that is found in nature. In particular, ^{191}Os , with a 15.4 d half-life, may be encountered because of its use in generators for producing ^{191m}Ir for medical imaging.

Iridium (Ir, Z = 77) is the second member of the series. It has two stable isotopes, ^{191}Ir and ^{193}Ir , and more than 30 radioactive isotopes in the range ^{182}Ir to ^{198}Ir . Because of its short half-life (4.96 s), ^{191m}Ir is used for radionuclide angiography. Based on physical properties, however, the isotope ^{192}Ir has been used for metabolic studies to assess biological behavior and exposure.

Metallic platinum (Pt, Z = 78) is used in manufacturing, its salts are used for numerous catalytic and industrial purposes, and platinum-containing organic compounds have been used as antineoplastic drugs. Because they are so commonly encountered, substantial metabolic and toxicologic information has been obtained concerning these materials. Platinum has six stable isotopes within the range ^{190}Pt to ^{198}Pt , and more than 20 radioactive isotopes, ^{169}Pt through ^{201}Pt , including naturally occurring ^{190}Pt . The physical properties of ^{191}Pt have led to its use in studies of biological behavior.

A.63.1 Biological Information

Neither osmium, iridium nor platinum are normal constituents of the human body. Because data from direct measurements are not available, absorption characteristics and biological behavior of osmium have been inferred from experimentally determined information concerning iridium.

Based on measurements of uptake from the GI tract in experimental animal species, fractional values of about 0.01 are obtained with orally administered ^{192}Ir and ^{191}Pt as chlorides. The ICRP (1980) noted that one study reported the absorption of carrier-free iridium to be less than 0.001 while an earlier report from same group indicated a value of about 0.1. The fractional absorption

values (f_1) of all compounds of these three elements is considered to be 0.01 (ICRP, 1980; 1981).

The ICRP review of reported experiments indicates that iridium concentrations in liver, kidney and spleen are ten-fold greater than those in the average whole body after intraperitoneal or intravenous administration to rats. With both osmium and iridium, 20 percent of the material leaving the transfer compartment is considered to immediately enter excreta. Partition of osmium and iridium in the normal human adult is taken as liver, 20 percent; kidney, 4 percent; spleen, 2 percent; and 54 percent is uniformly distributed throughout remaining organs and tissues.

After intravenous injection in rats, experiments found elevated concentrations of platinum in kidney relative to average total body and concentrations were increased to a lesser extent in liver, spleen and adrenal (ICRP, 1981). Another experiment found renal deposition after oral exposure to diets supplemented with stable platinum sulfate. Rats have relatively elevated concentrations in kidney and in bone after inhalation of the metal.

ICRP (1981) assumes the partition of platinum from the transfer compartment in humans to be: excretion, 20 percent; kidney, 10 percent; liver, 10 percent; spleen, 1 percent; adrenal, 0.1 percent; with the remainder uniformly distributed with an 8 d retention for 45 percent and 200 d for 5 percent.

A.63.2 Fetal/Placental Information

No direct data were located relative to the behavior of osmium or iridium during gestation. Their placental transfer and partition in the embryo/fetus are assumed to resemble those given for platinum.

As indicated, extensive measurements of absorption, excretion, retention and distribution were made after intratracheal, oral and intravenous administration of ^{191}Pt in saline to male rats (Moore *et al.*, 1975b). These studies included an additional group of pregnant rats at 18 dg that were given 925 kBq intravenously and killed 24 h later. Excretion (19 percent) was about the same as in adult males during the first day after injection. The average fetal concentration at 24 h was 0.01 percent dose per gram body weight, the fetal liver had a concentration of 0.05 percent dose per gram and the placenta had a concentration of 0.92 percent per gram.

Most tissue concentrations in the females were slightly less than in males but the value of 0.35 percent per gram of the administered platinum in maternal blood was only about one-third of that

in adult males at this same time and it was not until two weeks that this retention level was reached. These values are consistent with other maternal tissue concentrations (expressed as percent administered dose per gram) of 0.3 in bone, 0.6 in lung, 1.44 in liver, and 4.22 in kidney as well as with the above-noted 0.92 percent per gram placental concentration. Thus, only small amounts of injected platinum in rats enter the embryo/fetus while most of the metal enters and is retained in the placenta. The total activity in the fetal/placental mass may amount to nearly 10 percent of the injected radioactive material and there could be an indeterminately large fraction in the yolk sac and other membranes that could account for quantitative differences between pregnant females and adult male rats.

Placental transfer might also be inferred from the observation that administration of platinum salts to pregnant mice resulted in altered postnatal development, although neither placental transfer nor platinum content of the fetuses and offspring was measured (D'Agostino *et al.*, 1984). Administration of the sulfate led to decreased body weight of offspring in the period from 8 to 45 d post-partum and sodium hexachloroplatinate led to decreased activity levels but the effects could have been mediated through maternal effects.

Experimental studies using metallic platinum as an intrauterine contraceptive device in rats and rabbits led to decreased frequency of blastocyst implantation. Other experiments involving insertion of metallic platinum wire in the rat uterus after implantation had occurred (this does not expose the conceptus to platinum ions), did not decrease fetal survival (Chang *et al.*, 1970). These studies were directed toward investigations of mechanical contraception and should not be interpreted as providing evidence regarding placental transfer of platinum.

A.64 Gold

Gold (Au, Z = 79) has a single stable isotope, ^{197}Au , and over 20 radioisotopes in the range ^{186}Au to ^{203}Au . Probably the most important isotope from the standpoint of exposure is ^{198}Au , which has been used as a stabilized colloid in clinical medicine.

A.64.1 Biological Information

Gold is not a significant constituent of the human body and does not play any known role. Gold content of the body is given as less than 9.8 mg but no data on daily intakes are presented for Reference Man (ICRP, 1975). Based on a range of reported experimental values from 0.03 to 0.13, ICRP (1980) adopted an f_1 value of 0.1 for GI absorption of all compounds.

Stable gold has been incorporated in compounds such as gold sodium thiomalate and used to treat arthritis. This compound is retained in the body with a 3 d biological half-life, and similar values are found for other gold salts. ICRP assumes that gold entering the transfer compartment is uniformly distributed throughout all organs and tissues where it is retained with a biological half-life of 3 d. It is also assumed that the concentration in urine in the bladder is ten-fold the tissue concentrations at all times after exposure, and the urine content of the bladder is taken as 200 cm³ for dose calculations.

The behavior of ¹⁹⁸Au in colloidal form, as used in nuclear medicine, is described in ICRP Publication 53 (ICRP, 1987). It is assumed that there is no redistribution or excretion of the short half-lived gold that is administered in this form.

A.64.2 Fetal/Placental Information

High doses of gold compounds are teratogenic in rats and rabbits (Szabo *et al.*, 1978a; 1978b). Significant maternal toxicity was seen in these studies and it was not clear whether it was gold that entered the embryo that was responsible for the abnormalities. Even lower doses of gold yielded embryotoxic effects, however, which suggested that there might have been placental transfer and direct action.

Measurements of women who received therapeutic administration of stable gold compounds during pregnancy demonstrated that there was placental passage of these agents in the human although controlled studies have not been reported. Rocker and Henderson (1976) detected small deposits of gold in the liver and kidney of a 20-week fetus, as well as the placenta, from a woman who had been receiving therapeutic injections of sodium aurothiomalate.

Cohen *et al.* (1981) measured gold in blood samples from a woman who continued receiving 100 mg monthly intramuscular injections of this agent throughout a normal pregnancy. Venous serum gold levels at delivery were 3.92 µg mL⁻¹ and the

simultaneous umbilical cord level was $2.25 \text{ }\mu\text{g mL}^{-1}$, indicating substantial transfer of the gold. A study of 119 pregnancies in which women were exposed to gold during the first trimester detected children from two pregnancies who had minor anomalies; the authors discussed relationships between blood levels and teratogenicity (Miyamoto *et al.*, 1974).

A.64.3 Radiation Dose Estimates

The assumed ten-fold increase in relative concentrations of radioactivity in urine that was in the bladder at all times after exposure to gold salts has implications for calculating dose from maternal activity external to the embryo/fetus. Radioactive ^{198}Au colloid has been injected into the peritoneal and thoracic cavities for therapy of membrane effusions and intravenous injection has been made for reticuloendothelial deposition (Mahon *et al.*, 1973). Neither situation results in self-dose for the embryo/fetus but should be considered from the standpoint of external exposure from localized radioactive deposition sites in the mother.

A.65 Mercury

Mercury (Hg , $Z = 80$) has seven stable isotopes in the range ^{196}Hg through ^{204}Hg , and more than 20 radioactive isotopes, ^{177}Hg to ^{206}Hg . Radioisotopes of importance include ^{197}Hg , with a half-life of 64 h, that has been employed clinically in the chloride form for evaluation of the kidney. This radioisotope and ^{203}Hg are possibly relevant for exposure of the embryo/fetus.

A.65.1 Biological Information

Mercury is found as a trace constituent of the human body but does not seem to have a normal biological function. Mercury content of soft tissues of Reference Man is 13 mg and daily intakes are given as 0.015 mg (ICRP, 1975). The biological behaviors and effects of organic mercury compounds differ from those of inorganic compounds and the absorption of organic compounds is substantially greater. ICRP adopted an f_1 value of 0.02 for all inorganic compounds, an f_1 value of 1.0 for methylmercury and 0.4 for other organic compounds (ICRP, 1980; 1987).

The highest concentrations of inorganic mercury are found in the kidney (ICRP, 1980). In normal adults, kidney deposition is

40 percent, with 15 percent in liver and 45 percent in remaining tissues. The assigned values of biological retention half-lives are 40 d (95 percent) and 10,000 d (5 percent) (ICRP, 1980), but these were expressed as 1 d (80 percent) and 10 d (20 percent) in ICRP Publication 53 (ICRP, 1987).

Of organic compounds leaving the transfer compartment, 8 percent is assumed to go to kidney, and 20 percent to brain, and the remainder is uniformly distributed among the remaining tissues. Based on methyl mercury, 95 and 5 percent of tissue mercury are assumed to be retained with 80 and 10,000 d half-lives, respectively. Other compounds such as neohydrin are lost more rapidly, so that these times may be unduly conservative.

A.65.2 *Fetal/Placental Information*

Elemental mercury and its organic compounds are considered as agents of concern relative to reproductive effects. Reviewers have recognized that pregnant women treated with mercurials had a high incidence of spontaneous abortion (Alfonso and DeAlvarez, 1960). Exposure of pregnant rodents to high concentrations of mercury vapor by inhalation or to inorganic mercury compounds by mouth led to high stillbirth rates and increased incidences of congenital anomalies and neonatal mortality among the offspring (Berg, 1982). Malformations were generally minor and might have resulted from general maternal or fetal toxicity rather than to a specific teratogenic action.

Pregnant rats were injected with mercury nitrate or methyl mercury at times during late gestation (Baglan *et al.*, 1974). Transfer was not measured but ratios of tracer in placenta to that in the pups was determined. The ratio was about one with organic mercury for all times while it was about eight with injection of the nitrate at 16 dg and even greater with injection at 18 or 20 dg.

The known release of mercury from amalgam dental fillings (Vimy and Lorscheider, 1985; Patterson *et al.*, 1985) led to a study in sheep that measured the release of radiolabeled mercury from dental amalgam fillings and its transfer to the fetus in late gestation (Vimy *et al.*, 1990). Blood samples from the ewes and fetuses contained ^{203}Hg within 2 d of placement of the amalgam fillings and the highest fetal concentrations (measurements beginning at 16 d) were found in the liver and pituitary gland and there was an increasing concentration in the placentas with time. Activity continued to increase with time in tissues of the fetus and the ewe.

Baglan *et al.* (1974) found significant correlations between levels of environmental mercury in maternal blood, placenta and blood of newborn human infants. Dental personnel working with mercury-containing amalgams may be chronically exposed to considerable mercury vapor which would be absorbed by the adult. Measurement of mercury levels in blood cells and plasma of dental personal and their newborn babies and comparisons with unexposed controls showed no meaningful differences. However, mercury levels in placentas and fetal membranes from dental assistants who were exposed during pregnancy were about twice those from nonexposed controls, a significant difference (Wannag and Skjaerasen, 1975).

The marked potential for reproductive toxicity of organic mercurials, such as methylmercury, is illustrated by the symptomology resembling cerebral palsy and microcephaly in newborns of the fishing village of Minimata, Japan (Muramaki, 1972; Matsumoto *et al.*, 1965). These abnormalities were caused by methyl mercury contamination of the fish eaten by the population and fetal toxicity has become known as "Minimata disease." A similar incident involved the poisoning of an Iraqi population with methyl mercury contaminated grain (Amin-Zaki *et al.*, 1976; Marsh *et al.*, 1980). Reports of similar congenital neurologic disease such as psychomotor retardation and cerebral palsy in infants exposed *in utero* from this population and other instances of food contamination by methyl mercury may be taken as presumptive evidence for the placental transfer of methyl mercury in the human (Koos and Longo, 1976; Snyder, 1971).

A.66 Thallium

Thallium (Tl, Z = 81) has two stable isotopes, ^{203}Tl and ^{205}Tl ; it has more than 20 radioactive isotopes, ^{184}Tl to ^{210}Tl , with half-lives ranging from seconds to years. Because of its clinical use, from the standpoint of exposure of the embryo/fetus, the most interesting isotope is ^{201}Tl together with contaminants ^{200}Tl and ^{202}Tl . The longer-lived isotope, ^{204}Tl has been used for experimental studies in animals.

A.66.1 Biological Information

Thallium is a normal trace constituent of Reference Man; the content of soft tissues is not presented but daily intakes are given

as 1.5 µg (ICRP, 1975). Thallium sulfate and nitrate are readily absorbed from the GI tract and f_1 is taken as 1.0 for all compounds (ICRP, 1981).

Thallium is used in medical imaging as well as in industry while some of its salts are used as rat poisons. As a consequence, biological disposition has been studied in experimental animal species and intravenously injected thallium has been evaluated in humans as well, with good agreement among reports. The ICRP model assumes that the element is instantaneously translocated from blood. Except for kidneys, which contain about three percent of the thallium activity, the remaining 97 percent is uniformly distributed throughout all organs and tissues. The rate of removal is considered to be the same for all tissues, with a biological half-life of 10 d in humans (ICRP, 1981; 1987).

A.66.2 Fetal / Placental Information

Studies in rats and mice measured placental transfer of thallium ions after feeding. These studies found a rapid rise in thallium concentrations in fetal tissues at about the same rate but to levels about one-tenth of those in maternal kidney; fetal concentrations were similar to those eventually reached in maternal brain (Ziskoven *et al.*, 1983). After intraperitoneal injection, ^{201}Tl rapidly entered the rat fetus reaching initial average concentrations slightly greater than maternal blood but one-fifth to one-tenth of most visceral organs other than kidney, which was the predominant site of early deposition (Rade *et al.* 1982; Sabbioni *et al.*, 1982). The whole-fetus concentration was about the same as maternal brain but one-third of maternal muscle and remained at this level for the 192 h of study; maternal and placental concentrations fell during this period.

Whole-body autoradiography after intraperitoneal injection of ^{204}Tl in the mouse demonstrated fetal activity by 15 min with maximum accumulation at 2 to 4 h. There was greater deposition in placenta and in fetal membranes than in the embryo/fetus throughout gestation (Olsen and Jonsen, 1982).

Intra-arterial infusion of ^{204}Tl sulfate in potassium-deficient and normal pregnant rats led to progressive increases in maternal serum and fetal concentrations with infusion rate and time, which extended through a maximum of 32 min. In both groups, maternal blood plasma concentrations were approximately one-half of those in the erythrocytes, but were about 15-fold greater than the concentrations in the fetuses (Gibson and Becker, 1970).

A case report by Johnson (1960) indicated that there was no detectable thallium in the placenta or in the cord blood and urine of a baby born to a woman who had ingested rat poison several weeks previously. The woman's urine still contained a small amount of thallium at term and patches of alopecia on the baby's scalp indicated that the thallium had crossed the placenta.

A review by Barlow and Sullivan (1982) included this and several other cases of thallium ingestion by pregnant women, mostly attempts at suicide or to induce abortion. Data from controlled studies on human thallium exposure during pregnancy were not located, although it appears from the symptomatology, especially alopecia, that thallium crosses the placenta.

A.67 Lead

Lead (Pb, Z =82) is a toxic metal and exposures to stable lead may derive from sources ranging from additives in gasoline to lead pipes, storage batteries, lead-based paints, and wood preservatives. Stable lead serves as a benchmark for general and developmental toxicology evaluations because exposure of pregnant animals during organogenesis results in prenatal mortality and a characteristic complex of malformations and it is neurotoxic during childhood. Its radioisotopes have been used in experimental assessments of placental transfer and there are radiological health concerns about lead radioisotopes that are important decay products of radium and radon.

The most abundant naturally occurring isotopes of lead are stable, ^{206}Pb , ^{207}Pb and ^{208}Pb , but there are more than 20 radioactive isotopes in the range ^{184}Pb to ^{214}Pb , with half-lives ranging from fractional seconds to years. Based on physical characteristics and formation by decay of polonium or bismuth in the body of the woman or the embryo/fetus, of greatest relevance for evaluating placental transfer and exposure of the embryo/fetus are ^{209}Pb , ^{210}Pb , ^{212}Pb and ^{214}Pb .

A.67.1 Biological Information

Lead is a trace constituent of the human body but it is not involved in normal metabolic or biochemical processes. Lead content of the skeleton and total body of Reference Man are 110 mg and 120 mg, respectively; daily intakes in food and water are given as 0.44 mg (ICRP, 1975). There is greater GI absorption but more

variation among lead compounds than of lead. ICRP (1993) adopted the value of f_1 as 0.2 for ingestion between meals.

ICRP Publication 67 (ICRP, 1993) presents a detailed biokinetic model for lead. By way of summary, after injection, the primary deposition sites of ^{210}Pb are the red blood cell mass (55 percent), bone (10 to 15 percent), and liver (15 percent) with the remainder to the soft tissue compartments. There is redistribution from the red cells to excretion, soft tissues, and skeleton. There is tenacious retention only in mineral bone and lead can be substituted in the calcium positions of apatite and probably distributes rapidly throughout the volume of mineral bone.

A.67.2 Fetal/Placental Information

Data from studies in a variety of animal species demonstrate that lead can be readily transferred across the placenta to the fetus (Baglan *et al.*, 1974; Neathery and Miller, 1975). Several studies were performed by McClain and colleagues. In one representative experiment they intravenously injected rats at 17 dg with 50 mg kg^{-1} lead nitrate and killed them at intervals to collect maternal blood and tissues and fetuses for lead analyses (McClain and Becker, 1975). Blood and plasma concentrations declined exponentially, which was paralleled by a decrease in placental concentration. Fetal lead concentration increased through the 24 h study, reaching a final value of $8.1 \pm 0.3 \mu\text{g g}^{-1}$ of whole fetus (roughly 0.05 percent dose per gram) as compared to $13.1 \pm 3.1 \mu\text{g g}^{-1}$ in placentas. In another experiment, maternal blood samples and fetuses were removed at intervals during a 1 h period of intravenous infusion. The final concentration was $2.4 \mu\text{g g}^{-1}$ in whole fetuses as compared to $310 \pm 30 \mu\text{g mL}^{-1}$ in maternal blood plasma.

The effect of chelating agents on kinetics and fetal contents were studied by injection or infusion of ^{210}Pb in rats at 18 dg (McClain and Siekierka, 1975). The lead-chelate complex crossed the placenta more readily than did lead nitrate but was excreted from the pregnant rat more rapidly, so that fetal content was not increased. Injection of a bolus of 50 mg kg^{-1} of lead nitrate, a condition similar to that used in their earlier study, also resulted in fetal concentrations of about $8 \mu\text{g g}^{-1}$ at 1 and 2 d post-exposure. The corresponding concentrations in the placentas were about 22 and $11 \mu\text{g g}^{-1}$, respectively.

Hackett *et al.* (1982a; 1982b) and Hackett and Kelman (1983) reported that lead metabolism (blood clearance, tissue distribution, fetoplacental concentrations) and toxicity were affected by dosage

level and route of administration in pregnant rats exposed by gavage, inhalation or intravenous injection. In a comparison of intravenous dosages (5 and 25 mg kg⁻¹ lead nitrate or carrier-free ²¹⁰Pb), Hackett *et al.* (1982b) also found that fetoplacental contents and distribution and toxicity were affected by the presence of carrier and dosage level.

The relationship between the amount of lead administered and its content in the egg cylinder after injection at 9 dg was especially complex. However, 0.013 percent dose per gram at 1 d after injection of the tracer lead alone may be considered as a typical value. At 1 d after injection at 15 dg, the concentrations (percent dose per gram) of the two higher doses were about 0.11, 0.09 and 0.17 in the whole fetoplacental unit, fetus and placenta, respectively. Allowing for dose dependence, these results are in general accordance with those reported by McClain and his colleagues for the same stages of gestation.

Hackett *et al.* (1982b) found that autoradiographic activity was associated with embryonic structures, yolk sac, and decidua at early times after injection at 9 dg. By 1 d after injection at 15 dg, the placenta, Reichert's membrane, and visceral yolk sac contained label. There was also labeling of the fetal liver and chondrogenic areas; this increased with time. Carpenter *et al.* (1973) previously had reported similar patterns of diffuse activity in the fetus, but observed that there was relatively more autoradiographic activity associated with the placenta and membranes after injection of hamsters at 7 to 8 dg hamsters. The results of Hackett *et al.* (1982b) indicated that this pattern was attributable to the presence of ²¹⁰Po in the injection medium.

Clearance from maternal to fetal circulation was directly measured in a perfused guinea pig placental preparation. A value of $47 \pm 4 \mu\text{L min}^{-1}$ was obtained but the authors indicated that the circulating lead may have affected maternal blood flow to the placenta and that the true clearance may have been higher (Kelman and Walter, 1980).

Stillbirths and miscarriages have been recognized as common in populations of women who used lead salts as pottery glazes (Scanlon, 1975). It is known that lead is transferred across the human placenta to the fetus and this transfer can be monitored as early as the 12th week of gestation (Barltrop, 1969). Measurements of lead levels in maternal and neonatal blood samples found that mean concentrations in maternal blood were significantly higher in women from urban than from rural environments, but were not related to stage of gestation (Gershnik *et al.*, 1974). Overall mean

concentrations in neonatal cord blood ($0.094 \pm 0.037 \mu\text{g Pb mL}^{-1}$) were similar to those in maternal blood ($0.105 \pm 0.038 \mu\text{g Pb mL}^{-1}$). There was a high correlation between lead levels in mothers and corresponding infants in a subgroup of 98 paired samples.

Roels *et al.* (1978) likewise found a statistically significant correlation between concentrations of lead in cord and maternal blood. They also detected a weaker, but significant correlation with the concentration in the placenta. These authors tabulated reported results on placental lead concentrations. Their value ($0.084 \pm 0.051 \mu\text{g Pb mL}^{-1}$) was similar to those of many other workers, although some groups had reported up to a four-fold greater placental concentration.

Most studies find that concentrations are not related to stage of gestation, and overall mean concentrations in neonatal cord blood are similar to those in maternal blood. There is a high correlation of lead levels in blood of mothers and corresponding infants, as well as highly significant correlations between lead concentrations in cord and maternal blood, and a weaker, but statistically significant correlation with the concentration in the placenta. It has been suggested that there is mobilization of lead stored in bone during pregnancy and that the elevated maternal blood concentration could make it available for placental transfer (Manton, 1985; Russell and Calder, 1986; Thompson *et al.*, 1985).

Cumulated radiation doses to the embryo/fetus in the range of 3 to $6 \mu\text{Gy}$ were calculated to result from maternal injection of 37 kBq of ^{210}Pb at any stage of gestation.

A.68 Bismuth

Bismuth (Bi, Z = 83) has no stable isotopes although the most abundant isotope, ^{209}Bi , has a half-life in excess of 1,019 y. Among more than 20 other radioactive isotopes, ^{210}Bi , which predominantly emits beta rays and has a 5 d half-life, is an important parent and daughter in the uranium series that is encountered following decay of radon and is considered to be of primary relevance to exposure of the embryo/fetus. Also of interest is ^{212}Bi , an alpha-beta emitting radionuclide with a 1 h half-life, while ^{206}Bi , with a half-life of 6.24 d, is the common tracer radioisotope used for biological studies.

A.68.1 Biological Information

Bismuth is a trace constituent of the human body and the content of soft tissues of Reference Man is less than 0.23 mg, with a normal daily intake of 20 µg (ICRP, 1975). ICRP takes the value of f_1 as 0.05 for ingestion on the basis that basic salts of bismuth are poorly absorbed (ICRP, 1980; 1994). GI absorption of stable bismuth salts has been of interest relative to the possibility of exposure during pregnancy though the oral use of nonprescription agents containing bismuth subsalicylate (*e.g.*, Pepto Bismol®).

Based on a report by Russ *et al.* (1975) that bismuth is rapidly cleared from blood, the clearance half-life from the transfer compartment is considered to be 0.01 for all compounds. It is assumed that 30 percent of bismuth leaving the transfer compartment goes directly to excreta, 40 percent goes to kidney, and 30 percent is uniformly distributed throughout all other tissues (ICRP, 1980). Of the bismuth that enters tissues, 60 percent is assumed to be retained with a biological half-life of 0.6 d and 40 percent with a 5 d half-life. Other information regarding absorption from parenteral sites as well as pharmacology and toxicology are described by Stemmer (1976) while kinetic details and a model are given by Vienet *et al.* (1983).

A.68.2 Fetal/Placental Information

Bioavailable bismuth has been shown to be concentrated in the placenta but some is transferred to the fetus (Thompson, 1941). Reviews conclude that, under physiological conditions, bismuth entering the fetus binds to numerous tissues, especially growth fronts of bone (Reynolds, 1982; Stemmer, 1976).

Despite markedly different conditions, generally compatible results were obtained by Richardson (1992) who performed a limited study in pregnant guinea pigs that were killed 1 h after an intracardiac injection of $^{207}\text{BiCl}_3$. The measured placental concentrations were about the same as maternal blood but much greater than in whole fetuses. The concentration was elevated in fetal spleen at mid-gestation and in fetal femur at mid- and late-gestation.

One animal study reported that one of four sheep born of ewes fed 5 mg kg⁻¹ bismuth during gestation was stunted, hairless and exophthalmic but that there were not detectable levels of bismuth in tissues of the ewe or lamb (James *et al.*, 1966). Reports were not

found suggesting that nonprescription agents containing bismuth subsalicylate are associated with developmental toxicity.

A.69 Polonium

Polonium (Po, Z = 84) does not have any stable isotopes. There are about 30 naturally occurring radioactive isotopes, ^{193}Po to ^{215}Po , with half-lives ranging from a fraction of a second to 1,000 y. Polonium is primarily an alpha-emitting daughter product of radon that then decays to lead. The most important commonly encountered isotope, ^{210}Po , emits alpha rays and has a 138 d half-life.

A.69.1 Biological Information

Traces of polonium are found in the human body; no data are given for Reference Man but the reference daily intake is given as 0.1 Bq (ICRP, 1975). Data from measurements of tissues were used in ICRP Publication 30 (ICRP, 1979) to estimate that the total ^{210}Po content of the body as 40 Bq, with about 60 percent in mineral bone (ICRP, 1979). This activity primarily results from *in situ* production from ^{210}Pb and only minimally represents distribution of ingested or inhaled polonium.

The f_1 value for GI absorption from dietary sources is given as 0.5 in ICRP Publication 67 (ICRP, 1993). Polonium, as a decay product of radon, is especially encountered as deposits on particulates and also is detected in tissue after *in situ* decay of radon. Polonium has been reported to deposit in lung tissue after inhalation of cigarette smoke. The distribution is considered to be 30 percent in liver, 10 percent each in kidney and red bone marrow, 5 percent in spleen, and 45 percent in other tissues (ICRP, 1993). Retention halftime is taken as 50 d in all tissues.

A.69.2 Fetal/Placental Information

Results of human measurements, as below, corroborate the pattern seen in animal studies that found that minimal fractions of polonium salts pass into the fetal tissues. Lacassagne and Lattes (1924) reported that the greatest autoradiographic deposition of polonium was found in the chorionic villi of the rabbit placenta at 6 d after intravenous injection. There was a gradation of amounts in various maternal organs but there was practically no polonium in the fetus.

Söremark and Hunt (1966) performed whole-body and microscopic autoradiographic studies that included pregnant mice intravenously injected with single doses of ^{210}Po . Substantial activity remained in the blood throughout the 5 d study period; there were substantial concentrations in spleen, liver and lung, but the heaviest labeling was over the kidneys, especially cortex. There was relatively little labeling of the placenta at early times but activity subsequently increased to levels similar to the renal cortex. Polonium associated with the fetus was not seen through 4 d post-exposure but low activity was seen at 5 d. They reported only slight activity over the fetal sac membranes (amnion presumably) but it appears that there was substantial activity over the visceral yolk sac.

Inferential evidence from subsequent experimental studies confirms the placental deposition and lack of appreciable transfer of injected ^{210}Po . In pilot studies using an equilibrium mixture of ^{210}Pb and ^{210}Po in rats, Hackett *et al.* (1982b) found intense autoradiographic labeling of the placenta, Reichert's membrane, and visceral yolk sac. The intensity of the labeling was much less when they injected freshly separated ^{210}Pb , indicating that the greatest fraction of the autoradiographic label was derived from the polonium component. As noted above, Carpenter *et al.* (1973) had found high levels of activity in these same structures in their experiments using an equilibrium mixture of lead. The foregoing result suggests that the explanation for their findings is that the labeling was attributable to the ^{210}Po rather than to the ^{210}Pb .

Harrison *et al.* (1991) have reviewed earlier published data and provided results from more recent experiments that determined concentrations in hematopoietic tissues, in particular. In addition to confirming and quantifying deposition in placenta and in fetal membranes, deposition in the embryo/fetus was measured in these studies. These results were used for dose calculations that extended earlier estimates by Stather *et al.* (1984), and included calculations of dose to hematopoietic elements.

Analyses of specimens of Arctic lichens and grass, reindeer and caribou, and postpartum human placentas measured elevated levels of radionuclides, especially ^{210}Po and ^{210}Pb (Holtzman, 1966). This activity results from natural fallout and concentration by the slow-growing grasses and the animals. These results are compatible with other observations in human tissues, where elevated concentrations have been measured in placentas from populations who consumed reindeer and caribou meat (Hill, 1966). This again represented natural fallout radioactivity resulting from ^{222}Rn . There

was excellent correlation with ^{137}Cs , which was also produced in the atmosphere by decay of the fission product ^{137}Xe , and illustrated the role of the food chain.

A.69.3 Radiation Dose Estimates

It may be assumed that there would be minimal transfer to the embryo/fetus of ^{210}Po (or other isotopes) from the body of the pregnant woman and essentially no radiation dose. However, the placenta and membranes would receive some deposition from any polonium in her circulation. Polonium could be formed within the conceptus by decay of radon and its progeny, such as ^{210}Pb , and there would be subsequent decay of the ^{210}Po .

A.70 Astatine

Astatine (At, Z = 85) is a halide with more than 20 short-lived radioactive isotopes in the range ^{200}At to ^{219}At . The few isotopes found in nature result from decay of isotopes of uranium and thorium but others may be produced by heavy particle bombardment.

By analogy with the lighter halides, an f_1 value of one is assigned for ingestion of all compounds of astatine. Early reports indicated a metabolic similarity to iodine and there were indications of thyroidal deposition. By analogy with chlorine and bromine, it is assumed that astatine leaving the transfer compartment is uniformly distributed throughout all organs and tissues and is retained with a biological half-life of 10 d (ICRP, 1981).

No reports were found that present information on placental transfer or deposition in the embryo/fetus.

A.71 Radon

Radon (Rn, Z = 86) is a radioactive gas that is generated by decay of radium in the actinium, thorium and uranium series. Half-lives of the natural isotopes range from a small fraction of a second to the 3.8 d alpha-ray emitting ^{222}Rn , which is of primary importance for exposure of the embryo/fetus.

A.71.1 Biological Information

Peterman and Perkins (1988) proposed a kinetic model that provides a basis for estimating equilibrium specific activities of inhaled radon and its daughters in the human. The resulting values predict that the highest organ activity concentration values would be in lung, followed by kidney and liver, and a lower value in the femur. As a consequence of their high partition coefficient for lipids, fat and fatty tissues would have the greatest concentrations.

A.71.2 Fetal/Placental Information

Most of the direct data on early effects of high-level exposure as well as inferential information about placental transfer have been derived from the study reported by Bagg (1922). Sodium chloride was sealed into a container with an amount of radon, "radium emanations," originally equivalent to 18.5 GBq or 0.5 g radium. The radon-exposed salt was then dissolved in water to produce isotonic saline that was subcutaneously or intravenously injected into pregnant rats at various stages of gestation.

Bagg did not measure placental transfer but inferred that radon crossed the placenta because fetal death and macroscopic hemorrhages of the placentas or fetuses occurred within 24 h after intravenous injection of higher doses during late gestation. Although radon progeny could have been involved, the inferences are consistent with studies that showed that inhaled ^{85}Kr freely crosses the placenta in both directions, and that its concentration is the same in maternal and fetal blood. Bagg (1922) also obtained similar results when the rats were injected subcutaneously, as early as three weeks before mating. Explanations for such effects range from placental transfer of radon decay products to maternal toxicity produced by the earlier exposure; there is not a clear basis for choosing among alternatives.

Quantitative deposition was determined as part of an evaluation of the developmental toxicity of prolonged inhalation exposures of pregnant rats to high concentrations of radon and radon progeny (Sikov *et al.*, 1992c). Specific activities of ^{214}Pb in tissues of the pregnant rats were determined after 13 consecutive day-long exposures and the corresponding dose equivalent rates were calculated from the measurements made on the last day of exposure. Although not predicted by the Peterman and Perkins (1988) ^{222}Rn model, lung had the greatest activity concentrations and dose rates; the measured specific activity was almost

1,000 times greater than predicted because of inhalation of radon progeny along with radon gas.

The specific activities in the kidney were next highest but were more than an order of magnitude lower than in lung. Many of the nuclides in the radon decay chains are excreted through the kidney, which accounted for this organ having the highest specific activity of the other tissues and organs evaluated. The measured activity was markedly higher than predicted on the basis of only inhaled radon, but the differential was substantially less than with the lung, presumably because of a lesser role of inhaled radon progeny. Concentrations in other tissues such as the femur and liver were several-fold lower than in kidney.

Radionuclide concentration in the placenta was similar to that in the femurs and livers of the pregnant rats. Specific activity in the fetus was about one-third of that in the placenta; the concentration difference between components of the fetoplacental unit on the last day of exposure (19 dg) contrasted with the results with ^{85}Kr in rats, where concentrations were more uniform and fetoplacental radiation doses were similar to those received by tissues of the pregnant rats. These differences are interpreted as indicating that radon decay products are not freely transferring to the conceptus during and after inhalation exposures to radon.

Measurable quantities of radon daughters do cross the placenta and enter the fetus even though there is probably some sequestration of these decay products in the placental tissues. Most decay products formed in the fetus would tend to remain there. Available information (Sikov, 1987) indicates that placental transfer from the woman's blood would vary among specific nuclides although differences among factors such as decay schemes and short half-lives require consideration of interspecies differences in length of gestation.

Tentative conclusions derived from these limited measurements suggest that dose equivalent rates at the end of a prolonged inhalation exposure essentially mirror measured specific activities, and reflect the reduced levels of translocated radon decay products in the fetus. The fetoplacental unit receives radiation doses that, at maximum, are no higher than the dam because its concentrations were no higher than those in soft tissues of the dam and much less than lung and fat. The calculated dose rates to fetoplacental structures may not be applicable at early gestational stages, when the placenta and fetus are less well developed.

Reports on radon daughters in human abortuses and placentas include radioanalysis and autoradiography studies of lead, bismuth

and radium (Henshaw *et al.*, 1988; Richardson, 1992; Richardson *et al.*, 1991). These measurements, together with dosimetric calculations for human tissues and with results of experimental studies of effects on stem cells led to suggestions that there could be long term consequences of such perinatal inhalation exposures.

These descriptions suggest that some radon decay products cross the placenta and enter the fetus. Among these are polonium and other nuclides that show marked deposition in placental structures, with varying accessibility of blood activity to the fetus. On the contrary, it is not known to what extent these other nuclides are formed *in situ* by decay in the fetal compartment or cross the placenta in either direction (Harrison *et al.*, 1992).

A.72 Francium

Francium (Fr, Z = 87) has almost 30 isotopes; all are radioactive with half-lives of less than 30 min. The 22 min half-lived ^{223}Fr is found in nature, in conjunction with its parent ^{227}Ac .

By analogy with potassium, rubidium and cesium, f_1 is taken to be one for all compounds of francium (ICRP, 1981). It is assumed to be uniformly distributed throughout all organs and tissues and, in light of the short half-lives, to be retained indefinitely.

No information was found regarding the placental transfer of francium.

A.73 Radium

Radium (Ra, Z = 88) is a naturally occurring alkaline earth metal that includes about 25 isotopes in the range ^{206}Ra to ^{230}Ra . All of the isotopes are radioactive with half-lives extending from less than a second to 1,000 y. Most radium radionuclides are alpha emitters, although some emit beta particles. The most abundant in the environment is ^{226}Ra , in the uranium series, which spontaneously decays to ^{222}Rn . The isotopes ^{224}Ra , ^{220}Ra and ^{228}Ra are of primary interest and/or relevance to exposure.

A.73.1 Biological Information

Reference Man has a radium content of 31 pg, of which 27 pg are in the skeleton; daily intake in food and fluids is given as 2.3 pg (ICRP, 1975). Reported fractional uptakes of radium present in

drinking water or food are in the 0.15 to 0.21 range and f_1 is taken to be 0.2 for all compounds of radium (ICRP, 1993).

Task groups of the ICRP as well as individual groups of investigators have extensively modeled the behavior of the alkaline earth elements including radium (Leggett, 1992a; ICRP, 1993). The subsequent radon in soft tissue and bone, as well, have been considered in the resulting radiation doses. The model assumes that radon formed in soft tissue is lost from the body and retention and decay in bone varies with the time that the radium had been present in the tissue. The shorter lived isotopes of radon are assumed to remain with their parents.

After intravenous injection, radium follows the general pattern for calcium although exchange rates among compartments differ. There is substantial early redistribution that leads to urinary and fecal excretion. Early distribution considers 25 percent in bone and as much as 20 percent in soft tissue compartments. These are followed by decreases during the following months.

A.73.2 Fetal/Placental Information

Wilkinson and Hoecker (1953) dissolved $^{226}\text{RaCl}_2$ in saline and allowed the solution to reach equilibrium. Rats were intraperitoneally injected with the solution at 15 dg and killed for evaluation at 20 dg, but no radioactivity was detected in the placentas or fetuses. However, it is not clear whether and to what extent the nuclide was absorbed into the maternal blood from this route of administration. The finding of no transfer does not corroborate studies of human materials, which vary quantitatively among themselves but uniformly find fetal burdens of radium.

Martland and Martland (1950) evaluated 17 children from 10 mothers who had been employed as radium dial painters. Some of the mothers had sufficiently great radium burdens that they subsequently became symptomatic. Burdens of less than 10^{-8} g of radium were measured in the children, which the investigators considered to be in the normal range.

Rajewsky *et al.* (1965) measured the ^{226}Ra content of bones and soft tissue of approximately 200 human fetuses as well as 40 additional placentas at various stages of gestation. They found that the specific activity of bone ash (0.37 mBq g^{-1}) was independent of the stage of gestation, and was identical to that measured in adult bone. Concentrations ($3.7 \mu\text{Bq g}^{-1}$) were similar in fetal soft tissues and the placentas and did not change throughout gestation.

Increasing fetal mass during gestation led to a concomitant increase in the total content of the fetuses.

Analyses have been performed on the skeletal remains of a former radium dial painter who had died from complications of pregnancy and on her seven month fetus (Schlenker and Keane, 1987). They estimated that about 0.06 percent of the radium in the mother had been mobilized and transferred to the fetal skeleton during the seven months of gestation, based on total ^{226}Ra contents of 100 kBq and 63 Bq, respectively. Based on radium per gram of calcium measurements of 96 and 6.5 in maternal and fetal bone, an estimate of 3.2 Bq of radium per gram of calcium in the woman's plasma at the time of pregnancy, and factors from ICRP models, they calculated a 1.4-fold greater placental transfer of radium relative to calcium.

It thus seems that radium concentrations in fetal and maternal bone are similar and that the concentration ratio is one, especially for multiple occupational and/or continued environmental exposures. Progressive differences in bone composition relative to stage of gestation would influence deposition and the associated radiation doses. There would be concurrent changes in the size and shape of anatomical features and their relationships would interact with composition.

A.74 Actinium

Actinium (Ac, Z = 89) is an actinide element with more than 20 isotopes, all radioactive and in a range ^{209}Ac to ^{232}Ac with half-lives from the undeterminablely short to 21.8 y. Actinium isotopes occur in nature as members of the thorium and neptunium series as well as the actinium series.

Based on reviews and experimental studies, ICRP (1981) assumed the value of f_1 to be 0.001 for all compounds. Available experimental data show that after intravenous or intramuscular injection, actinium is concentrated in liver and skeleton, and kidney to a lesser extent; accordingly, the metabolic model for plutonium was considered applicable. It was assumed that of actinium leaving the transfer compartment, 45 percent was translocated to each of mineral bone and liver and retained with biological half-lives of 100 y in bone and 40 y in liver. Small fractions are considered to go to the gonads, where it remains indefinitely, and the remainder goes directly to excreta.

No information relative to placental transfer or deposition in the embryo/fetus was located.

A.75 Thorium

Isotopes of thorium (Th, Z = 90) are found in all four of the heavy radioactive series and ^{232}Th , a 1.4×10^{10} y half-life alpha emitter, is the initial member of the thorium series. There are over 20 isotopes, ranging from ^{223}Th to ^{234}Th , all radioactive with half-lives ranging from a fraction of a second to 7.54×10^4 y (^{230}Th).

A.75.1 Biological Information

Thorium contents are not given for Reference Man although there are studies that indicate that mineral bone contains about 30 μg . Daily intake in food and fluids is given as 3 μg . Based on experimental data and comparisons with chemically similar elements, ICRP Publication 69 (ICRP, 1995) takes f_1 to be 0.0005. That report presented a detailed biokinetic model for thorium that assumed that thorium is cleared from blood with a biological half-time of 0.5 d. Of this, 70 percent is deposited in bone, deposited on bone surface, and slowly transferred throughout the volume. Another 30 percent is deposited in soft tissue compartments, including liver, and then returned to blood.

A.75.2 Fetal/Placental Information

As reported by Maurer *et al.* (1950) and Engels *et al.* (1950), pregnant rats at stages from 14 to 20 dg were intravenously injected with 4 mg of natural thorium plus about 185 kBq ^{234}Th . Analyses of tissues from rats killed 30 min to 5 d later demonstrated rapid blood clearance. Placental content rose rapidly to about 0.3 percent of the injected activity and remained constant thereafter; specific activities in the embryo/fetus also were independent of sampling interval beyond 3 h. Fetal concentrations were dependent on stage of gestation at exposure, decreasing from 0.001 percent dose per gram after injection at 14 dg to about 0.0001 percent dose per gram after injection at 19 to 21 dg. The authors stated that these values were 10^3 - to 10^6 -fold greater than for Thorotrast®, a colloidal suspension of thorium dioxide used as a contrast medium. From the data, they calculated a descriptor of the

ability of the placenta to pass thorium; the resulting values displayed a similar stage-dependent pattern.

Weiner *et al.* (1985) determined the levels of environmental thorium in human fetoplacental tissues obtained from legal abortions, and compared the measurements with data on concentrations in normal adult females. The samples were categorized as: first trimester (10 to 14 weeks post conception); second trimester (22 to 24 weeks); and early third trimester (26 weeks). There were detectable amounts of thorium in five of the seven first-trimester samples and the highest measured fetal concentration was 39 dpm kg^{-1} , with a corresponding placental concentration of only 4.4 dpm kg^{-1} . They did not report detectable thorium levels in older fetuses.

A.76 Proactinium

The actinide proactinium (Pr, Z = 91) is formed through nuclear reactions as well as by decay in the neptunium, uranium and actinium series. There are no stable isotopes but there are more than 15 radioisotopes ranging from ^{215}Pr to ^{238}Pr with half-lives from less than a second to 3×10^4 y.

No data concerning proactinium is given to Reference Man (ICRP, 1975). By analogy with other actinides, the value of f_1 is considered to be 0.0005 for all compounds (ICRP, 1981). The metabolic model, based on studies in rats and a human accident case, assumes that of proactinium leaving the transfer compartment, 40 percent is translocated to skeleton where it is retained with a biological half-life in excess of 100 y. Deposition is assumed to be 15 percent in the liver and 2 percent in kidneys. Retention in liver has two components with biological half-times of 10 d (70 percent) and 60 d (30 percent).

No fetal deposition or placental transfer information was located.

A.77 Uranium

Uranium (U, Z = 92) has 15 isotopes, ^{227}U to ^{240}U , all of which are radioactive. Uranium compounds have been used for a variety of industrial applications; effects have been reported but all seem to be related to the chemical toxicity. From the radiological standpoint, the three most frequently encountered isotopes are ^{238}U (4.5×10^9 y), the initial isotope in the uranium series, and the two naturally occurring alpha-ray-emitting radioisotopes that are used

in nuclear reactions: ^{234}U (2.4×10^5 y) and ^{235}U (7×10^8 y). These isotopes, together with ^{233}U (1.59×10^5 y), which is often used as prototype for experimental studies, are of greatest dosimetric interest relative to exposure of the embryo/fetus.

A.77.1 Biological Information

Reference Man gives the daily intake in food and fluids as 1.5 µg and the uranium content of the body as 90 µg, with 59 µg in skeleton and 7 µg in the kidneys (ICRP, 1975). The metabolism and toxicity of uranium compounds have been extensively studied in adults of various species and ICRP Publication 69 (ICRP, 1995) assigned a fractional absorption value of 0.02 for dietary forms of uranium. That report, which uses the model of Leggett (1994), provides a biokinetic model for hexavalent uranium that is based on data from animal studies as well as human data from occupational exposures, after injection of terminally ill patients, and analyses after ingestion at normal dietary levels (ICRP, 1995). As a general summary, the model considers that about 63 percent of uranium from plasma is rapidly excreted and 17 percent goes to kidney where 5 percent is tenaciously retained and 12 percent is excreted with a 7 d halftime. It is also assumed that 15 percent goes to mineral bone compartments and the remainder is distributed through the rest of the body.

A.77.2 Fetal/Placental Information

Despite the extensive information about uranium in adults, relatively few data are available concerning its placental transfer or developmental toxicity. Sikov and Mahlum (1968) analyzed maternal and fetoplacental tissues from rats that had been intravenously injected with approximately 444 kBq kg⁻¹ of ^{233}U citrate at 15 or 19 dg and killed 24 h later. The concentrations in the fetuses on the day following injection at the two times were on the order of 0.01 and 0.03 percent dose per gram, respectively. After injection at 19 dg, fetal liver and kidney concentrations were higher than the whole fetus concentration and concentration in the fetal femur was even more markedly elevated.

Sikov and Rommereim (1986) subsequently studied distribution and effects in rats that received intravenous exposure to citrated solutions of ^{233}U at 9, 15 or 19 dg at dosages of 66.6, 122.1, 212.75 and 370 kBq kg⁻¹. Exposure at 9 and 15 dg produced dose-dependent trends toward increased prenatal mortality, decreased

fetal and placental weights, and increased malformation frequency. The highest fetoplacental concentration (0.066 percent dose per gram), represented by the egg cylinder, was found on the following day when exposure was done at 9 dg (organogenesis). Concentrations in the embryo/fetus and the placenta progressively decreased thereafter, but the concentration in the fetal membranes remained relatively constant. The concentrations in the fetuses at 1 d after injection at 15 or 19 dg (0.004 and 0.009 percent dose per gram) were slightly lower than in the previous experiment, but selective deposition in fetal bone and liver was again observed. The placental concentrations were 0.024 and 0.036 percent dose per gram at 1 d after injection at the two times, respectively, and the corresponding values for the fetal membranes were 0.18 and 0.39 percent dose per gram.

Weiner *et al.* (1985) measured significant concentrations of ^{234}U in three of seven first trimester samples from human abortuses that were evaluated in their determinations of environmental actinides. The concentrations were similar in fetal and placental tissues, and the highest concentration was about 1.6 dpm kg $^{-1}$ ^{234}U . Among 16 second trimester samples, 12 were positive for ^{234}U . When all uranium isotopes were summed for positive samples, a concentration range of 0.097 to 0.32 dpm kg $^{-1}$ was found for the fetuses, 0.31 to 0.52 dpm kg $^{-1}$ for the placentas, and 3.5 to 3.8 dpm kg $^{-1}$ for the umbilical cords. The concentration in their reference adult was 2.1 dpm kg $^{-1}$ and they concluded that the fetus did not selectively concentrate uranium.

Estimated cumulated radiation absorbed doses through the time of birth from maternal intravenous injection of 37 Bq during fetal stages are in the range of 0.1 to 0.5 mGy. Estimated dose rates to the embryo/fetus for these uranium isotopes (^{234}U , ^{235}U and ^{238}U) are dependent on stage of gestation when introduced into the mother's blood and time periods after intake (Sikov and Hui, 1996).

A.78 Neptunium

Neptunium (Np, Z = 93) does not occur in nature but is an important activation product associated with the nuclear fuel cycle. There are more than 10 isotopes which range from ^{228}Np to ^{242}Np with half-lives of a few minutes to two million years. Some of these isotopes also result from decay of extraction products so that neptunium is primarily encountered in reactor waste. Of potential interest relative to the need for secure storage, are ^{237}Np , ^{238}Np

and ^{239}Np , with half-lives of 2.14×10^6 y, 2.12 d, and 235 d, respectively.

A.78.1 Biological Information

Information concerning neptunium is not given for Reference Man. Experiments show that fractional absorption of the nitrate from the GI tract of rats is about 0.01 but absorption may be lower by a factor of 10 when the element is present in trace quantities or incorporated in food. A GI absorption factor, f_1 , of 0.0005 was adopted in ICRP Publication 67 (ICRP, 1993).

Some reports suggested that skeletal neptunium may distribute like calcium, but most data indicate that its metabolic behavior is more similar to that of plutonium, and that is the model applied to neptunium (ICRP, 1993). About 32 percent of neptunium leaving the circulation is assumed to go directly to excretion *via* the kidneys. A total of 45 percent is translocated to mineral bone where it is retained with a multi-year biological half-life, and 10 percent goes to liver compartments and is retained with a 2 y effective biological half-life. The remainder goes to soft tissue compartments with a removal halftime of 1 d for redistribution.

A.78.2 Fetal/Placental Information

Sikov and Mahlum (1968) intravenously injected rats after 14 or 19 dg with about 370 kBq kg^{-1} of ^{237}Np , in citrate at a 2.5 molar ratio. Radioanalysis of tissues collected 24 h later determined that the fetuses had average concentrations on the order of 0.01 and 0.02 percent dose per gram, respectively, at the two times of injection. The highest concentrations in the 20 dg fetuses were found in the femurs and kidneys, 0.41 and 0.23 percent per gram, respectively. As a basis for comparison, the concentrations in the corresponding organs of their dams were 1.9 and 3.6 percent dose per gram. The placental concentrations were 0.04 and 0.18 percent dose per gram at the two times but the corresponding concentrations in fetal membranes were substantially higher: 0.81 and 1.24 percent dose per gram.

In conjunction with a study on fetal toxicity, Moskalev *et al.* (1969) intravenously injected rats at 13, 16 or 19 dg with 22.6 kBq g^{-1} of ^{237}Np in a nitrate solution and made measurements 2 d later. The neptunium content of the fetuses did not vary uniformly with stage of gestation although fractions in the placentas tended to increase. Rough calculations, based on assumptions of weights and

litter sizes, suggest that the corresponding concentrations in the fetuses were 0.006, 0.001 and 0.003 percent dose per gram with injection at the three times, while placental concentrations were substantially higher: 0.4, 0.2 and 0.5 percent dose per gram, respectively.

Intravenous injection of rats with 11.1 to 185 kBq kg⁻¹ ²³⁷Np as the oxalate increased the incidence of preimplantation mortality. Relative to controls, offspring of litters receiving these doses showed a greater depression of erythrocyte production after gamma irradiation, prolonged narcosis after hexanol administration, and decreased sexual function (Ovcharenko and Fomina, 1982).

A.79 Plutonium

Plutonium (Pu, Z = 94) does not exist in nature but is produced by neutron and heavy particle bombardment. It has been used in nuclear weapons and breeder reactors and has received limited use in long-lived power sources. There are about 15 known isotopes of plutonium ranging from ²³²Pu to ²⁴⁶Pu, with half-lives from fractions of a second to 8.2×10^7 y for alpha-emitting ²⁴⁴Pu. Based on their use for comparative purposes and the likelihood of being encountered, the isotopes of greatest interest are ²³⁷Pu (45.12 d half-life), ²³⁸Pu (87.74 y), and ²³⁹Pu (2.44×10^4 y).

A.79.1 Biological Information

Reference Man does not contain plutonium but weapons testing and occupational exposures have resulted in measurable quantities in food and human tissues. The limited human data generally are in accord with data from studies in experimental animals. The biological disposition of plutonium is probably the most thoroughly studied of the actinides and its behavior is often taken as being representative of this group of elements. There is little absorption of most common chemical forms of plutonium from the GI tract or lung. The values of f_1 in ICRP Publication 30 (0.00001 for oxides and hydroxides and 0.0001 for all other commonly occurring compounds) have been adjusted several times in subsequent publications. For exposure via environmental sources a value of 0.0005 for GI absorption was adopted in Publication 67 (ICRP, 1993). This same value of f_1 also has been adopted for the elements of higher atomic number (ICRP, 1994).

The models of plutonium distribution are based on the biokinetics for actinides described by Leggett (1985; 1992b). Following entry into the circulation, plutonium is assumed to be distributed according to the age-related descriptions given in ICRP Publications 56 and 67 (ICRP, 1989; 1993). In adults, 50 percent is translocated to bone surface with internal redistribution, and 30 percent is deposited in liver compartments. The retention at early times typically is viewed as effectively being 2 to 3 y, which is long relative to gestation. A small percentage of the plutonium goes directly to early excretion but there is additional clearance to urine and feces from the liver and soft tissue compartments. About 15 percent goes to soft tissue compartments, *i.e.*, to all soft tissues excluding the liver and the gonads, which also receive and retain a small fraction.

A.79.2 *Fetal/Placental Information*

Numerous investigators have examined the placental transfer, fetoplacental distribution, and developmental toxicity of plutonium. Animal experiments have shown that plutonium crosses the placenta after injection in pregnant animals, that there are quantitative changes relative to stage of gestation, and that it can be transferred to offspring *via* lactation (Harrison *et al.*, 1991; Morgan *et al.*, 1992; Sikov, 1987).

Finkel (1947) found that neonates from viable litters that were born to mice that had been injected with ^{239}Pu before mating or at various times during the last 5 dg each contained a small percentage of the administered dosage. She found an increased incidence of totally stillborn litters and of stillbirths in viable litters. The newborn offspring each contained about 0.02 percent of the administered dosage but the concentration values, 0.02 to 0.06 percent dose per gram, tended to decrease with increasing dosage and with decreased time between injection and measurement. Concentrations at birth were markedly less (<0.005 percent dose per gram) in litters from dams injected before mating.

Generally consistent patterns of placental transfer and distribution have been reported when rats were injected during organogenesis. The embryos continue to accumulate plutonium from maternal plasma during the 3 d after injection of ^{239}Pu , but at 9 dg the concentrations decrease because of their continued growth. In an experiment with typical results, 12 dg rat embryos had concentrations of about 0.03 percent dose per gram but concentrations declined to about one-tenth of that level by 20 dg (about 0.002

percent dose per gram) even though their masses had increased more than 100-fold (Rommereim and Sikov, 1986; Rommereim *et al.*, 1985). The placental concentrations were higher than in the embryo initially and did not display as great a decrease; representative values were 0.15 and 0.048 percent dose per gram at these two times of determination. Concentrations in the fetal membranes (including the yolk sac) were even higher and did not display a decrease with time (0.35 percent dose per gram). Parallel series of experiments have been performed by other investigators and yielded generally compatible results (Morgan *et al.*, 1991; Levack *et al.*, 1994b).

Higher doses of plutonium are embryotoxic when injected in rats at 8 to 10 dg, presumably through effects on the yolk sac. In contrast to the embryotoxicity associated with exposure during this period of organogenesis, intravenous injection of rats with markedly greater amounts at fetal stages (15 or 19 dg) did not affect prenatal development.

The patterns of fetoplacental partition at later stages are similar to those at earlier stages although there are stage-related quantitative differences in fetoplacental tissue concentrations. The cited experiments of Rommereim also provide representative values for fetoplacental concentrations after intravenous injection during later gestation. At both 1 and 5 d following exposure at 15 dg, and at 1 d after injection at 19 dg the fetal concentrations were about 0.03 to 0.04 percent dose per gram. Total plutonium contents were higher at 20 dg, reflecting the greater fetal masses and also indicating that the fetus accumulated additional plutonium as a consequence of progressive skeletal development between 16 and 20 dg. After injection at 15 dg, the concentration was 0.68 percent dose per gram at 16 dg but declined to 0.3 percent dose per gram by 20 dg, while injection at 19 dg yielded a concentration of 1.2 percent dose per gram at 20 dg. The concentrations in the fetal membranes were markedly higher; the values were 5.5 percent dose per gram at 1 d after injection at 15 dg and declined to 2.8 percent dose per gram by 5 d postexposure. On the day after injection at 19 d, the concentration in the membranes was even higher, nine percent dose per gram.

The biological disposition pattern of plutonium also involves stage-dependent changes in patterns of deposition and localization in the developing skeleton, and in metabolism relative to that of the pregnant animal. Plutonium primarily deposits on bone surfaces of adult animals, in contrast to calcium, strontium and radium, which are incorporated into the matrix of the bone. In the fetus, there is a

progressive, relatively rapid burial in compact bone matrix as a result of remodeling (Sikov and Mahlum, 1976).

Autoradiographic studies during these periods of gestation also show the highest fetoplacental concentrations of plutonium to be in the fetal membranes, especially the developing yolk sac and the highest concentration over the fetus involved the skeleton (Ullberg *et al.*, 1967). The placenta contained lower concentrations and the embryo/fetus even less. The concentration in the yolk sac may be as much as 10 to 100 times greater than the average membrane concentration because it represents only a small portion of the total mass. Autoradiographic and radioanalytic studies from several laboratories have extended and quantified the findings, but are in general accord with these early observations. The villous yolk sac is a persistent and functional structure in rodent embryos, but its function is more transient in most other mammalian species. Autoradiographic studies have consistently found that the highest concentrations of plutonium (and of many other heavy elements) in the embryo/fetal membranes is deposited in this structure.

Studies to examine the partition of ^{239}Pu at various stages of gestation in rabbits showed a species difference in its distribution in the pregnant animals (Kelman *et al.* 1982). The concentrations in the placentas and fetal membranes were not as high as those found in rodents and the ratio of concentrations between these two structures and in comparison to the embryo/fetus was not as high in rats and mice. Limited studies were performed in guinea pigs because of their greater maturity near term and to provide a comparison with perfusion studies to be described below. They were injected at 60 dg and killed at 61 dg; concentrations were lower than in other species although the pattern of partition was similar (Kelman and Sikov, 1981). Comparable differences have been reported by Morgan *et al.* (1991) and Levack *et al.* (1994b).

Andrew *et al.* (1977) performed studies to determine if yolk sac deposition also occurs during early gestation of nonhuman primates. They intravenously injected pregnant baboons with 370 kBq kg^{-1} of citrated ^{239}Pu at representative stages of gestation and removed the uteri and their contents 24 h later. The uterus and fetoplacental components were dissected and subjected to radioanalysis. The various concentration ratios were similar to those found in the rodent; findings have been generally confirmed by Paquet *et al.* (1998). The autoradiographic localization of radioactivity was also similar in the two species when allowance was made for morphologic differences. The yolk sac, which could be visualized in embryos at 23 dg, had marked autoradiographic label.

Kelman and Sikov (1981) directly measured placental transfer using perfusion of the near-term guinea pig placenta after injection of citrated ^{239}Pu into the maternal circulation. Placental transfer was calculated in terms of clearance, which was found to be $2.3 \mu\text{L min}^{-1}$, the lowest clearance previously measured with this system. They found a reduced clearance of a tracer dose of tritiated water at the highest doses of plutonium, indicating that the maternal blood supply to the placenta was interrupted. The threshold for this effect was about 185 kBq kg^{-1} body weight.

Hackett *et al.* (1977) measured ^{239}Pu levels in fetoplacental units of rats at 20 dg that were mated four weeks after injection. There was little mobilization from the maternal tissues, and only about 0.2 percent of the original dose (roughly 0.003 percent per gram) was present in the products of conception. Green *et al.* (1979) injected mice with ^{239}Pu , as the citrate, mated them 1 d later, and analyzed the offspring at birth. Each neonate contained about 0.015 percent of the administered dose. The amount transferred decreased throughout subsequent pregnancies of the injected mice, reaching approximately 0.002 percent per neonate by their ninth litter.

Studies have examined the role of physicochemical state and total administered mass on actinide transfer. Sikov and Mahlum (1976) compared fetoplacental concentrations at 24 h after intravenous injection of 37 kBq doses ($\sim 148 \text{ kBq kg}^{-1}$) of citrated ^{237}Pu , ^{238}Pu and ^{239}Pu at 15 or 19 dg. Even though the specific activities of the three isotopes were markedly different, concentrations in the three component structures (membranes, placenta, fetus) were similar to those found in other experiments and there were no consistent deposition differences. Weiss and Walburg (1978) intravenously injected mice at 16 dg with graded amounts of ^{239}Pu and killed them 48 h later. Concentrations in the fetuses tended to be higher than measured in studies by others but they were clearly less than in the placenta, which was assayed with fetal membranes. The concentrations in both compartments were similar after administration of two lower doses (about 0.8 percent dose per gram in fetus and 9 percent dose per gram in placenta), but were about two- to four-fold lower, respectively, after injection of the higher dose.

Prenatal human tissues have been analyzed from subjects who received chronic exposures at environmental levels. The reported concentrations and ratios for embryo/fetus, placenta and adult differ with gestational stage and between groups of investigators. The relative fetal concentration values for plutonium, as calculated

from data of numerous studies in various animal species, differs from ratios reported after the limited numbers of radioanalyses of human tissue.

One set of determinations compared measurements on tissues from abortuses, products of conception, and unrelated adults (Weiner *et al.*, 1985). They were not able to detect significant amounts of plutonium isotopes in first-trimester specimens. Measurable amounts of ^{239}Pu were found in six of the second trimester samples, with concentrations ranging from 0.11 to 2.06 dpm kg^{-1} . Summation of total plutonium from assays in one fetus gave a total value of 0.08 dpm, with a concentration of 0.23 dpm kg^{-1} . The corresponding values were 4.4 dpm and 0.07 dpm kg^{-1} in an average adult female, and the comparisons were taken as suggesting a three-fold concentration factor. The maximal ratio of concentration in umbilical cord to fetus was about 10, but placental concentrations apparently were not greater than those in the fetuses.

These findings were not quantitatively confirmed in studies by the National Radiological Protection Board (Bradley and Prosser, 1993; Prosser *et al.*, 1994). Using more sensitive methods, they analyzed several second trimester specimens from two geographical locations. They measured fetal levels of plutonium that were at or below the level of detection and estimated a concentration factor of less than 0.2. Although not found in pooled samples, in some specimens a higher placental concentration was measured than in the corresponding fetal sample; this is consistent with animal data described above.

Russell (1997) reported on a plutonium analysis of the umbilical cord and placenta from a worker who became pregnant and had a child several years after an accidental inhalation intake. Control samples were obtained from a nonindustry worker following birth of her child. The radiation worker had excreted measurable amounts of ^{239}Pu and ^{241}Am during the month after intake, but subsequent urinalyses had been below detection levels. The placenta from the worker had a concentration of 9.7 mBq kg^{-1} , which was about 150 times higher than the placenta from the control woman and eight times higher than the concentration they used for their reference woman. Umbilical cords were not weighed so concentrations were not calculated. The analyses found that there was 1.59 μBq in the cord from the worker but there was less than the minimum detection level (0.37 μBq) in the control sample.

A.79.3 Radiation Dose Estimates

Alpha radiation doses to the embryo at early stages, when it is embedded in the uterine mucosa, would be relatively homogeneous. These would be a small fraction of the average doses received by the pregnant woman, and an even smaller fraction of the dose to her tissues of primary deposition. High localized concentrations in the placental structures may result in radiation absorbed doses that are as great as or greater than those to any of the maternal tissues. Because of their short path length, alpha particles from extraembryonic areas would not reach the embryo, but beta emissions could irradiate embryonic areas.

Sikov and Hui (1996) estimated radiation dose rates and absorbed doses for 37 Bq of ^{238}Pu and ^{239}Pu introduced into the mother's blood at any of several stages of gestation and for different periods after intake. For both isotopes, cumulated doses received by the time of birth progressively increased from about 0.1 mGy with injection at two months of gestation to between 0.77 and 0.89 mGy with injection at eight months.

It is during the embryonic stages that extraembryonic deposition, in the yolk sac, has the greatest potential significance for producing early deleterious effects on the germ and hematopoietic cells. Stem cells, which later migrate into the embryo, may be affected and show later effects. The primitive blood cells should be considered for inclusion in estimates of dose to the hematopoietic system. Stather *et al.* (1984), Morgan *et al.* (1992), and Harrison *et al.* (1991) have published dose estimates that consider this in the hematopoietic dose.

A.80 Americium

Americium (Am, Z = 95) is formed both by heavy particle bombardment as well as radioactive decay of plutonium isotopes. Americium has more than 10 isotopes in the range ^{232}Am to ^{247}Am , all radioactive, with half-lives from less than 1 min to 7.37×10^3 y. The isotope of greatest interest is ^{241}Am , a 432 y half-life alpha-ray emitter.

A.80.1 Biological Information

Weapons testing and occupational exposures have resulted in measurable quantities of americium in human tissues, and there are substantial data from studies in experimental animals.

Americium absorption generally has been taken as representative of the actinide group of elements and ICRP adopted an f_1 value of 0.0005 in Publication 67 (ICRP, 1993).

Following entry into the transfer compartment, the ICRP metabolic model for americium is in accord with the biokinetic model for plutonium but there are some quantitative differences (ICRP, 1993). Accordingly, 30 percent is considered to be deposited in skeleton and tenaciously retained, with internal translocation among compartments. The 50 percent deposited in liver compartments also has a long net biological half-life. Another 10 percent is considered as going directly to excretion. The model allows for a translocation of americium to the gonads, where it is permanently retained, as well as to other soft tissue compartments.

A.80.2 Fetal / Placental Information

In a study of fetal toxicity, Moskalev *et al.* (1969) intravenously injected rats at 13, 16 or 19 dg with high doses of ^{241}Am in citrate solutions, and killed them 2 d later. The resulting average maternal to fetal concentrations (6:1 to 2:1) and the americium content of the fetuses and placentas varied with stage at injection. Rough calculations, based on assumptions of weights and litter sizes, suggest that the fetal concentrations were 0.03, 0.0005 and 0.07 percent dose per gram after of injection of the lower dose at the three times, respectively. The corresponding concentrations in the placentas were 0.21, 0.19, and 0.91 percent dose per gram, values that are consistent with those reported by subsequent workers.

These studies and those of Sikov and Mahlum (1968), among others, as well as subsequent workers, have shown that a smaller fraction of injected americium than plutonium entered the conceptus or fetoplacental unit. These studies found that there was proportionately less selective deposition of americium in the placenta and membranes relative to the ratios observed with plutonium.

Limited radioanalytic data obtained by Hisamatsu and Takizawa (1983) as part of an autoradiographic investigation are also consistent with these results. Estimations of fetal and placental concentrations from their data indicate concentrations of 0.0015 and 0.15 percent dose per gram, respectively, after injection at 15 dg. The corresponding concentrations were 0.004 and 0.21 percent dose per gram on the day following injection at 18 dg. Concentrations in the membranes were not presented, but it was evident from the autoradiographs that the membranes contained relatively increased levels of activity as well as differences between elements.

Transfer to the embryo/fetus and preferential placental deposition was less with americium than with plutonium.

Because previous comparisons were inferential, Rommereim and Sikov (1986) and Rommereim *et al.* (1985) measured the contemporaneous transfer and deposition patterns of ^{239}Pu and ^{241}Am . The data confirmed prior ^{241}Am values reported from their laboratory as well as the differences between the elements. Transfer to the embryo/fetus and preferential placental deposition were less with americium than plutonium.

The embryo had a concentration of 0.002 percent dose per gram at 12 dg when injected at 9 dg, which decreased to 0.0002 by 20 dg. The concentrations in the placenta and membranes were 10- to 15-fold higher than the embryo at 12 dg, and only decreased by a factor of two to three by 20 dg. At both 1 and 5 d after exposure at 15 dg, the fetal concentrations were 0.001 to 0.002 percent dose per gram but at 1 d after injection at 19 dg the fetal concentrations were about 0.032 percent dose per gram. After injection at 15 dg, the placental concentration was 0.11 percent dose per gram at 16 dg but declined to 0.073 percent dose per gram by 20 dg, while injection at 19 dg yielded a concentration of 0.26 percent dose per gram at 20 dg. The concentrations in the membranes were only slightly higher; the values were 0.08 percent dose per gram at 1 d after injection at 15 dg and declined to 0.06 percent dose per gram by 5 d postexposure. The concentration in the membranes was somewhat higher, 0.19 percent dose per gram on the day after injection at 19 dg.

Levack *et al.* (1994a) made analogous comparisons in rats and guinea pigs using ^{238}Pu and ^{241}Am . They also found a greater fetoplacental deposition of plutonium than of americium. The fraction of the administered ^{241}Am , measured at late gestation, was only slightly greater for the guinea pig than the rat even though litter sizes were smaller and fetal weights were proportionately greater. They calculated concentration ratios of 0.2 and 1.5 for the fetus and placenta, respectively, relative to the maternal average.

Weiss *et al.* (1980) studied the effect of mass administered on distribution and concentration in mice, using ^{243}Am , a longer-lived isotope. At 2 d after intravenous injection at 16 dg, concentrations in the fetus and placenta (assayed with membranes) were markedly less than those they had found with plutonium; both fetal and placental concentration varied only by a factor of two between the highest and lowest dosage. As in the earlier study they performed with plutonium (Weiss and Walburg, 1978), the measured concentrations were elevated relative to other investigators,

about 0.02 percent dose per gram in the fetuses and one percent dose per gram in the placentas.

Sikov and Kelman (1989) used an *in situ* placental perfusion system to quantify the placental transfer of ^{241}Am . Intravenous injection of 1.1 MBq kg^{-1} body weight did not affect maternal blood flow to the placenta. The measured clearance value ($3.4 \pm 0.7 \mu\text{L min}^{-1}$) was not significantly different from that measured previously for ^{239}Pu . However, clearance was significantly less than that of ^{239}Pu by a factor of five when corrections were made for the disrupted maternal blood flow that was produced by plutonium administration (Sikov and Kelman, 1989).

Placental transfer of ^{241}Am citrate was measured at 7 d after intravenous injection in two late gestation baboons (Paquet *et al.*, 1998). The fetuses had about 0.3 to 0.4 percent of the administered americium but the placentas had two to three percent. The placental concentrations were similar to those in maternal tissues but the concentrations in the fetal bone and soft tissues were about an order of magnitude lower than the corresponding maternal tissue.

In determinations of nuclide content after environmental exposure, Weiner *et al.* (1985) were not able to detect significant amounts of ^{241}Am in first trimester abortuses. Six of the second trimester samples contained measurable activity, with concentrations ranging from 0.08 to 0.29 dpm kg^{-1} in the fetuses. Substantially higher values, 1.0 and 2.1 dpm kg^{-1} , were measured in umbilical cords.

Radiation dose rates and absorbed doses for ^{241}Am introduced into the mother's blood at several stages of gestation and for different periods after intake were estimated by Sikov and Hui (1996). Cumulated doses through birth for administration of 37 Bq during the fetal period were on the order of 0.1 mGy. This value, as well as the underlying dose rate, was about five-fold less than the corresponding value with plutonium isotopes.

The calculations of Harrison *et al.* (1992) demonstrated that americium in the yolk sac also made significant contributions to radiation doses received by hematopoietic tissue. Their estimates indicated that the doses from ^{239}Pu , however, were more than 10-fold greater than the corresponding doses from ^{241}Am .

A.81 Curium

Curium (Cm, Z = 96) is formed through single and multiple neutron captures and by heavy particle bombardment of plutonium, as well as decay of other heavy radionuclides. It has 14 radioisotopes

between ^{238}Cm and ^{251}Cm . These include both alpha and beta emitters and half-lives that range from minutes to over 10^7 y.

A.81.1 *Biological Information*

Adequate quantities of curium have been available to allow for metabolic and other biological studies including GI absorption in rats, dogs and baboons. Based on these data and by analogy with americium, ICRP assumed f_1 to be 0.0005, and recommended that the americium model should apply to curium (ICRP, 1994).

A.81.2 *Fetal/Placental Information*

The fractions of administered ^{244}Cm in the fetoplacental unit were measured at several times during a study of the embryotoxicity produced by intravenous injection in rats at 9 dg (Sikov and Mahlum, 1975b). The concentration in the egg cylinder was about 0.08 percent dose per gram on the day following exposure. Concentrations in the embryo were 0.002 and 0.001 percent dose per gram at 3 and 5 d after injection (12 and 14 dg), respectively. The corresponding concentrations were 0.012 and 0.011 in the placenta and were 0.01 and 0.004 in the embryo/fetal membranes. To supplement measurement in toxicity experiments, concentrations were determined at 24 h following injection at 15 and 19 dg. The concentrations (percent dose per gram) at these two later times of gestation were 0.001 and 0.013 in the fetuses, 0.021 and 0.11 in the placentas, and 0.007 and 0.05 in the membranes.

A.82 Berkelium, Californium and Einsteinium

These elements, Bk, Cf and Es ($Z = 97, 98, 99$), are formed by interactions of heavy particles or neutron capture reactions with lighter elements such as americium and curium, as well as radioactive decay. Each has several radioisotopes that include both beta and alpha emitters. Californium also has isotopes that emit neutrons and it undergoes spontaneous fission.

A.82.1 *Biological Information*

Adequate quantities of these elements have been produced to allow for metabolic and other biological studies. Sufficient amounts

of californium were produced to evaluate its applicability to clinical medicine as a radiotherapeutic agent that would exploit its neutron emissions. No information is given in Reference Man and because there is relatively little other information concerning their biological behavior, aspects of expected behavior are extrapolated from data obtained for other actinides. By analogy with americium, fractional GI absorption values, f_1 , are considered to be 0.0005. Information is in general accord with ICRP recommendations and the metabolic model for americium has been applied to compounds of these elements.

A.82.2 *Fetal/Placental Information*

Very limited information in Hungate *et al.* (1972) suggests that the behavior of berkelium during pregnancy resembles americium but there are no data concerning californium.

Measurements available concerning the placental transfer of einsteinium are derived from a single study that was directed primarily as an evaluation of developmental toxicity. Rats were intravenously injected with an acidic solution of ^{253}Es , as the chloride, after 15 or 19 dg, and killed 24 h later (Sikov and Mahlum, 1972). Concentrations in the fetus (expressed as percent administered dose per gram) at the two times were 0.0022 and 0.008. Concentrations in the fetal liver and spleen were approximately the same as those in the whole fetus, but the concentration in the femur was almost 20-fold higher. Concentrations (percent dose per gram) were 0.253 and 0.757 in the placentas and 0.409 and 0.519 in the fetal membranes following injection at the two times of gestation. Examination of autoradiographs of placentas indicated that the concentration of einsteinium in the decidua was greater than in the labyrinth at both times and that there were high levels of localized activity in the trophoblast. Most of the activity in the fetal membranes was associated with the yolk sac and localization in these structures tended to be greater than with americium. The fraction of the injected dose that was deposited in the conceptus, however, approximated that found with ^{241}Am under similar experimental conditions. Thus, by analogy with GI absorption, placental transfer and the resulting prenatal concentration may be assumed to resemble americium.

A.83 Fermium and Heavier Elements

At least seven elements with atomic numbers of 100 and above have been produced in minute quantities, and there is evidence for the existence of yet heavier elements. Some isotopes, all radioactive with short half-lives, have been identified for those with atomic numbers through 107.

As with other heavy elements, biological behavior is predicted by analogy with americium.

Glossary

absorbed dose (D): The quotient of $d\bar{\epsilon}$ by dm , where $d\bar{\epsilon}$ is the mean energy imparted by ionizing radiation to matter of mass dm , thus the dose, D is:

$$D = \frac{d\bar{\epsilon}}{dm}$$

The unit of dose is the gray (Gy); formerly the unit was the rad (1 Gy = 100 rad). The term “dose” is often used in an informal way to mean effective dose, equivalent dose, or committed dose depending on the context.

absorbed fraction (ϕ): The fraction of the energy of type-i radiation emitted from any source organ that is absorbed in the target organ.

activity (A): A measure of the radioactivity that is proportional to the number of nuclear transitions per unit time.

activity, cumulated (\tilde{A}): The time integral of the activity, $\int [A(t)dt]$, which is proportional to the sum of all the nuclear transitions during a given time interval.

allantois: A sac-like diverticulum from the hindgut of amniote embryos.

amnion: The avascular membranous sac that immediately surrounds the amniotic fluid and embryo/fetus.

amniotic fluid: The fluid that is contained within the amnion.

annual reference levels of intake (ARLI): The activity of a radionuclide that, taken into the body during a year, would provide a committed effective dose to a person, represented by Reference Man, equal to 20 mSv. The ARLI is expressed in becquerels (Bq).

apoptosis: A process involving spontaneous self-destruction of cells; it plays a role in cell population kinetics and formation of structures of the embryo/fetus, as well as being a response to radiation injury.

becquerel (Bq): The special name for the unit of activity, $1 \text{ Bq} = 1 \text{ s}^{-1}$; formerly the unit was the curie ($1 \text{ Bq} \approx 27.03 \times 10^{-12} \text{ Ci}$).

biokinetic model: A series of mathematical relationships formulated to describe the intake, uptake and retention of a

radionuclide in various organs of the body and the subsequent excretion from the body by various pathways.

blastocyst: Developmental stage of most mammalian embryos that follows the morula; typically consists of a hollow sphere of trophoblast cells with an “inner cell mass” of formative cells.

blastomere: A cell of a cleavage stage or morula; excludes persisting cells of the polar body.

chorion: The outer fetal membrane that adheres to the uterine lining and surrounds the amnion.

cleavage: First few cell divisions of an ovum.

committed effective dose: The time integral of the effective dose rate from an intake of a radionuclide. Unless specified otherwise, the time interval is taken to be 50 y for those exposed in the workplace and 70 y for members of the public.

conceptus: General term referring to the entire products of conception, from the time the ovum is fertilized through the time of birth or parturition.

corticogenesis: The histogenic process by which the cerebral cortex of the brain is formed.

decidua: Specialized endometrial connective tissue that is differentiated during pregnancy in most mammals that have placentas; it represents maternal tissues that are expelled at parturition.

decidual basalis: Decidua at the base of the placenta, to which the placenta is attached.

deterministic effects: Effects for which the severity of the effect in affected individuals varies with the dose, and for which a threshold usually exists.

development: Expression used in embryology in reference to the normal growth and differentiation of a part or the whole of an embryo, fetus or child.

ectoderm: Outer germ layer of the embryo and chorion. It forms the epithelial lining of the amnion and all trophoblast derivatives, including epidermal structures and the nervous system.

effective dose: The sum over specified tissues of the products of the equivalent dose in a tissue (T) and the weighting factor for that tissue (w_T). That is,

$$E = \sum_T w_T H_T$$

where E is the effective dose and H_T is the equivalent dose to tissue T. The unit of effective dose is the sievert (Sv); formerly the unit was the rem, 1 Sv = 100 rem.

egg cylinder: The developing embryo, in the implantation chamber that is formed by swelling and closure of the endometrial crypt in which the fertilized egg lodged; usually pertains to rodents.

embryo: A developing vertebrate at stages from the first cleavage until the fetal period, cf. fetus.

endoderm: Inner germ layer of the embryo. It forms the lining of the gastrocoel, yolk sac, and their derivatives, including portions of the epithelium of the respiratory and digestive systems.

equivalent dose (H_T): A quantity obtained by multiplying the average absorbed dose in a tissue or organ by a radiation weighting factor (w_R) to allow for the different effectiveness of the various ionizing radiations in causing harm to tissue. The unit of equivalent dose is the sievert (Sv); formerly the unit was the rem, 1 Sv = 100 rem.

fetal membrane: General term for extraembryonic and extrafetal structures that are derived from the fertilized ovum. They are involved in the normal nourishment and development of the embryo/fetus. Examples include the chorion, amnion, yolk sac, and allantois, as well as the umbilical cord and placenta.

fetus: The developing conceptus, from the time that its external resemblance to the adult is sufficient to make it grossly recognizable as a member of the major taxonomic group to which it belongs until its time of hatching or birth (eight weeks in humans).

gestation: Maintenance of a developing embryo within the body of the parent, in a uterus, ovary or oviduct.

gray (Gy): The special name for the unit of absorbed dose, kerma and specific energy imparted, $1 \text{ Gy} = 1 \text{ J kg}^{-1}$. Formerly the unit was the rad, $1 \text{ Gy} = 100 \text{ rads}$.

histogenesis: The formation or development of tissues from the undifferentiated cells of the germ layers of the embryo.

implantation: Term most commonly referring to blastocyst adhesion and attachment to or embedment in the endometrium.

induction: The specific morphogenetic effect that is brought about by a (chemical) stimulus that is transmitted from one embryonic part to another.

mean absorbed dose (\bar{D}): The average energy per unit mass deposited in a target organ or tissue by ionizing radiation.

mental retardation: Congenital, but nonspecific reduction in cognitive capacities. *Severe mental retardation* is often used to signify an individual who is unable to perform simple

calculations, to make simple conversation, to care for himself or herself, or was or is institutionalized. Such individuals are generally found to have an intelligence test score which is less than 70 on conventional tests.

mesenchyme: Embryonic connective tissue derived from mesoderm.

mesoderm: Middle germ layer of the embryo. It gives rise to muscle, bone, connective tissue, and some epithelia and is also a component of some of the extraembryonic membranes.

microcephaly: Condition of abnormal smallness of the head, sometimes associated with mental defects.

monotocous: Giving birth to one offspring at a time.

morula: Globular solid mass of blastomeres formed by the initial cleavages of the zygote; period of embryonic development that precedes the blastula.

neuron: The nerve cell with its processes, collaterals and terminations; it is regarded as the structural unit of the nervous system.

organogenesis: Collective term used to refer to the sequence of processes by which the cells of the three primitive germ layers are organized into the primordial organ systems of the early embryo.

parturition: The process of giving birth.

physical half-life (T): The time in which one-half of the nuclei of a particular radionuclide decay.

pia (pial surface): The delicate fibrous membrane that closely envelops the brain and spinal cord.

placenta: Vascular, membranous structure that forms within the uterus from maternal and embryonic tissues during pregnancy; it provides communication between the woman and the embryo/fetus *via* the umbilical cord.

placenta-hemochorial: Placenta in which the trophoblast of the internal membrane is in direct contact with circulating maternal blood.

polytocous: Giving birth to several offspring at one time.

pregnancy: State of having an embryo/fetus within the body.

preimplantation period: Time between egg fertilization and the implantation of the embryo in the wall of the uterus.

radiation weighting factor (w_R): A factor used for radiation-protection purposes that accounts for differences in biological effectiveness between different radiations. The radiation weighting factor (w_R) is independent of the tissue weighting factor (w_T).

radioactivity: The property leading to spontaneous emission of radiation and broadly, the radiation so emitted.

Reference Man: Standardized descriptor of person with body size, anatomy, physiology and composition as given in ICRP Publication 23 (ICRP, 1975).

Reichert's membrane: Acellular mucoprotein layer between the trophoblast and endoderm of the placental disk; especially prominent in rodents with inverted yolk sacs.

residence time (τ): The average time that an administered radionuclide spends in the source organ.

SI: The International System of units.

somatopleure: A basic anatomical element of the vertebrate embryo/fetus and its membranes; composed of ectoderm and adjacent layers of somatic mesoderm. It gives rise to the chorion, amnion and the primitive embryonic body wall, cf, splanchnopleure.

somite: One of the many paired segmental masses of early mesoderm in vertebrate embryos that give rise to dermatomes, myotomes and sclerotomes.

source organ (h): The organ containing the radionuclide that is the source of the energy deposited in a target organ.

specific absorbed fraction (Φ): The absorbed fraction per unit mass of the target organ. $\Phi = \phi/m$, cf, absorbed fraction.

splanchnopleure: A basic anatomical element of the vertebrate embryo/fetus that is composed of endoderm and the adjacent inner layers of lateral plate (splanchnic) mesoderm. It gives rise to the allantois and the vascular areas of the yolk sac, muscles and the connective tissue of the wall of the gut and its derivatives (thyroid, respiratory tract, liver, stomach and intestines), cf, somatopleure.

stochastic effects: Effects, the probability of which, rather than their severity, is a function of radiation dose without threshold.

target organ or region (k): An organ for which the radiation absorbed dose is calculated.

teratogen: A substance or agent that tends to produce abnormal development and congenital malformations.

Thorotrast®: A proprietary contrast medium for roentgenography that contained a colloidal suspension of thorium dioxide.

tissue weighting factor (w_T): A factor that indicates the ratio of the risk of stochastic effects attributable to irradiation of a given organ or tissue (T) to the total risk when the whole body is uniformly irradiated.

transition: A nuclear change from one energy state to another, generally accompanied by the emission of particles or photons. Often called a decay, or disintegration.

trophoblast: (1) Extraembryonic ectoderm other than that lining the amniotic cavity and chorioamniotic duct. (2) Cytotrophoblast cell, including trophoblastic giant cells.

trophoblastic cell: Giant cells derived from trophoblast; they are usually mononucleate, but sometimes multinucleate.

umbilical cord: Vascular cord that connects a fetus to its placenta.

yolk sac: In placental mammals, it is a membranous sac with walls composed of endoderm and mesoderm that is attached to the embryo. The structure has the primary nutritional function prior to the elaboration of the placenta, and is the initial source of the primitive hematopoietic and germinal cells.

zygote: Fertilized ovum from the time of intermingling of the contents of the male and female pronuclei.

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The NCRP

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

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

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

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

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

- SC 1 Basic Criteria, Epidemiology, Radiobiology and Risk
 - SC 1-4 Extrapolation of Risk from Non-Human Experimental Systems to Man
 - SC 1-6 Basis for the Linearity Assumption
 - SC 1-7 Information Needed to Make Radiation Protection Recommendations for Travel Beyond Low-Earth Orbit
 - SC 1-8 Risk to Thyroid from Ionizing Radiation
- SC 9 Structural Shielding Design and Evaluation for Medical Use of X Rays and Gamma Rays of Energies Up to 10 MeV
- SC 46 Operational Radiation Safety
 - SC 46-8 Radiation Protection Design Guidelines for Particle Accelerator Facilities
 - SC 46-10 Assessment of Occupational Doses from Internal Emitters
 - SC 46-11 Radiation Protection During Special Medical Procedures
 - SC 46-13 Design of Facilities for Medical Radiation Therapy
 - SC 46-14 Radiation Protection Issues Related to Terrorist Activities that Result in the Dispersal of Radioactive Material
 - SC 57-10 Liver Cancer Risk
 - SC 57-15 Uranium
 - SC 57-16 Uncertainties in the Application of Metabolic Models
 - SC 57-17 Radionuclide Dosimetry Models for Wounds
- SC 64 Radionuclides in the Environment
 - SC 64-17 Uncertainty in Environmental Transport in the Absence of Site Specific Data
 - SC 64-18 Ecologic and Human Risks from Space Applications of Plutonium
 - SC 64-19 Historical Dose Evaluation
 - SC 64-20 Contaminated Soil
 - SC 64-21 Decontamination and Decommissioning of Facilities
 - SC 64-22 Design of Effective Effluent and Environmental Monitoring Programs
 - SC 64-23 Cesium in the Environment
- SC 66 Biological Effects and Exposure Criteria for Ultrasound
- SC 72 Radiation Protection in Mammography
- SC 75 Guidance on Radiation Received in Space Activities
- SC 85 Risk of Lung Cancer from Radon
- SC 86 Hot Particles in the Eye, Ear or Lung
- SC 87 Radioactive and Mixed Waste
 - SC 87-1 Waste Avoidance and Volume Reduction
 - SC 87-2 Waste Classification Based on Risk
 - SC 87-3 Performance Assessment
 - SC 87-4 Management of Waste Metals Containing Radioactivity

- SC 88 Fluence as the Basis for a Radiation Protection System for Astronauts
- SC 89 Nonionizing Electromagnetic Fields
 - SC 89-1 Biological Effects of Magnetic Fields
 - SC 89-3 Extremely Low-Frequency Electric and Magnetic Fields
 - SC 89-4 Modulated Radiofrequency Fields
 - SC 89-5 Biological Effects and Exposure Criteria for Radiofrequency Fields
- SC 91 Radiation Protection in Medicine
 - SC 91-1 Precautions in the Management of Patients Who Have Received Therapeutic Amounts of Radionuclides
 - SC 91-2 Dentistry
- SC 92 Public Policy and Risk Communication
- SC 93 Radiation Measurement

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

- American Academy of Dermatology
- American Academy of Environmental Engineers
- American Academy of Health Physics
- American Association of Physicists in Medicine
- American College of Medical Physics
- American College of Nuclear Physicians
- American College of Occupational and Environmental Medicine
- American College of Radiology
- American Dental Association
- American Industrial Hygiene Association
- American Institute of Ultrasound in Medicine

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United States Department of Transportation
United States Environmental Protection Agency
United States Navy
United States Nuclear Regulatory Commission

**United States Public Health Service
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The NCRP has found its relationships with these organizations to be extremely valuable to continued progress in its program.

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

Australian Radiation Laboratory
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Health Council of the Netherlands
Institute de Protection et de Surete Nucleaire (France)
International Commission on Non-Ionizing Radiation Protection
Japan Radiation Council
Korea Institute of Nuclear Safety
National Radiological Protection Board (United Kingdom)
National Research Council (Canada)
Russian Scientific Commission on Radiation Protection
South African Forum for Radiation Protection
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The NCRP values highly the participation of these organizations in the Special Liaison Program.

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- 11 *Dose Limits for Individuals Who Receive Exposure from Radionuclide Therapy Patients* (1995)
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- 15 *Evaluating the Reliability of Biokinetic and Dosimetric Models and Parameters Used to Assess Individual Doses for Risk Assessment Purposes* (1998)

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- 15 *Radiation Science and Societal Decision Making*, Proceedings of the Twenty-ninth Annual Meeting held on April 7-8, 1993 (including Taylor Lecture No. 17) (1994)
- 17 *Environmental Dose Reconstruction and Risk Implications*, Proceedings of the Thirty-first Annual Meeting held on April 12-13, 1995 (including Taylor Lecture No. 19) (1996)
- 18 *Implications of New Data on Radiation Cancer Risk*, Proceedings of the Thirty-second Annual Meeting held on April 3-4, 1996 (including Taylor Lecture No. 20) (1997)

Lauriston S. Taylor Lectures

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1	<i>The Squares of the Natural Numbers in Radiation Protection</i> by Herbert M. Parker (1977)
2	<i>Why be Quantitative about Radiation Risk Estimates?</i> by Sir Edward Pochin (1978)
3	<i>Radiation Protection—Concepts and Trade Offs</i> by Hymer L. Friedell (1979) [Available also in <i>Perceptions of Risk</i> , see above]
4	<i>From "Quantity of Radiation" and "Dose" to "Exposure" and "Absorbed Dose"—An Historical Review</i> by Harold O. Wyckoff (1980)
5	<i>How Well Can We Assess Genetic Risk? Not Very</i> by James F. Crow (1981) [Available also in <i>Critical Issues in Setting Radiation Dose Limits</i> , see above]
6	<i>Ethics, Trade-offs and Medical Radiation</i> by Eugene L. Saenger (1982) [Available also in <i>Radiation Protection and New Medical Diagnostic Approaches</i> , see above]
7	<i>The Human Environment—Past, Present and Future</i> by Merrill Eisenbud (1983) [Available also in <i>Environmental Radioactivity</i> , see above]
8	<i>Limitation and Assessment in Radiation Protection</i> by Harald H. Rossi (1984) [Available also in <i>Some Issues Important in Developing Basic Radiation Protection Recommendations</i> , see above]

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- 14 *Radiation Protection and the Internal Emitter Saga* by J. Newell Stannard (1990) [Available also in *Health and Ecological Implications of Radioactively Contaminated Environments*, see above]
- 15 *When is a Dose Not a Dose?* by Victor P. Bond (1992) [Available also in *Genes, Cancer and Radiation Protection*, see above]
- 16 *Dose and Risk in Diagnostic Radiology: How Big? How Little?* by Edward W. Webster (1992) [Available also in *Radiation Protection in Medicine*, see above]
- 17 *Science, Radiation Protection and the NCRP* by Warren K. Sinclair (1993) [Available also in *Radiation Science and Societal Decision Making*, see above]
- 18 *Mice, Myths and Men* by R.J. Michael Fry (1995)

Symposium Proceedings

No.	Title
1	<i>The Control of Exposure of the Public to Ionizing Radiation in the Event of Accident or Attack</i> , Proceedings of a Symposium held April 27-29, 1981 (1982)
2	<i>Radioactive and Mixed Waste—Risk as a Basis for Waste Classification</i> , Proceedings of a Symposium held November 9, 1994 (1995)
3	<i>Acceptability of Risk from Radiation—Application to Human Space Flight</i> , Proceedings of a Symposium held May 29, 1996 (1997)

NCRP Statements

No.	Title
1	"Blood Counts, Statement of the National Committee on Radiation Protection," <i>Radiology</i> 63 , 428 (1954)
2	"Statements on Maximum Permissible Dose from Television Receivers and Maximum Permissible Dose to the Skin of the Whole Body," <i>Am. J. Roentgenol., Radium Ther. and Nucl. Med.</i> 84 , 152 (1960) and <i>Radiology</i> 75 , 122 (1960)
3	<i>X-Ray Protection Standards for Home Television Receivers, Interim Statement of the National Council on Radiation Protection and Measurements</i> (1968)
4	<i>Specification of Units of Natural Uranium and Natural Thorium, Statement of the National Council on Radiation Protection and Measurements</i> (1973)
5	<i>NCRP Statement on Dose Limit for Neutrons</i> (1980)
6	<i>Control of Air Emissions of Radionuclides</i> (1984)
7	<i>The Probability That a Particular Malignancy May Have Been Caused by a Specified Irradiation</i> (1992)

Other Documents

The following documents of the NCRP were published outside of the NCRP report, commentary and statement series:

Somatic Radiation Dose for the General Population, Report of the Ad Hoc Committee of the National Council on Radiation Protection and Measurements, 6 May 1959, *Science*, February 19, 1960, Vol. 131, No. 3399, pages 482-486

Dose Effect Modifying Factors In Radiation Protection, Report of Subcommittee M-4 (Relative Biological Effectiveness) of the National Council on Radiation Protection and Measurements, Report BNL 50073 (T-471) (1967)
Brookhaven National Laboratory (National Technical Information Service Springfield, Virginia)

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