Report Rapport

Atomic Energy Control Board
Commission de contrôle de l'énergie atomique

INFO--0332

CA9200063

LITERATURE REVIEW OF THE STUDIES ON UPTAKE, RETENTION AND DISTRIBUTION OF RADIONUCLIDES BY THE FOETUS

by

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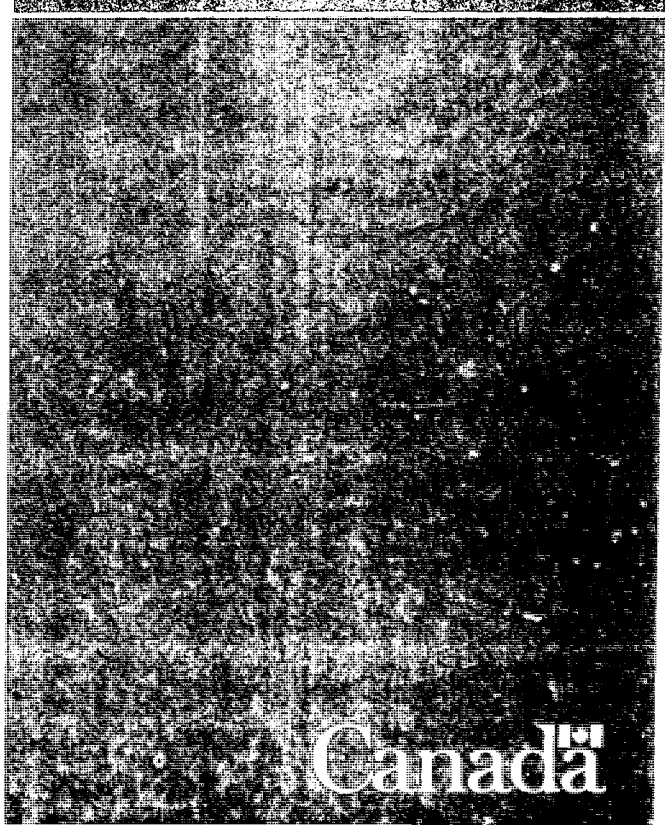

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LITERATURE REVIEW OF THE STUDIES ON UPTAKE, RETENTION AND DISTRIBUTION OF RADIONUCLIDES BY THE FOETUS

by

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A research report prepared for the
Atomic Energy Control Board
Ottawa, Canada

Project No. 7.099.1

October, 1989

Canada

Research report

LITERATURE REVIEW OF THE STUDIES ON UPTAKE, RETENTION AND DISTRIBUTION OF RADIONUCLIDES BY THE FOETUS

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ABSTRACT

This report summarizes the available literature from the last 10 years dealing with studies on uptake, retention and distribution of radionuclides by an embryo or foetus following maternal intakes. The review concentrates on isotopes commonly used by Canadian licensees. From the animal studies and from the limited human data, it is evident that after maternal contamination, the embryo or foetus accumulates and retains most radionuclides. Very little human data is available and a large fraction of the quoted values for human foetal dose retention are obtained from extrapolation from animal experiments. The information obtained in animal experiments is useful in determining general patterns of retention and distributions of radionuclides within the foetoplacental unit.

RÉSUMÉ

Le présent rapport résume les données de la documentation disponible des 10 dernières années portant sur les études sur l'apport, la rétention et la distribution des radionucléides dans les embryons et les foetus par suite de toute incorporation de la mère. Cette revue se concentre sur les isotopes les plus généralement utilisés par les titulaires de permis canadiens. D'après les études sur les animaux et les rares données sur les humains, il est évident que l'embryon ou le foetus accumule et retient la plupart des radionucléides dès que la mère a été contaminée. Il existe très peu de données sur les humains et une grande partie des valeurs de rétention des doses du foetus sont obtenues par extrapolation des études sur les animaux. Les renseignements acquis par ces études sur les animaux sont utiles pour déterminer les tendances générales de rétention et de distribution des radionucléides à l'intérieur de l'unité foeto-placentaire.

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LITERATURE REVIEW OF THE STUDIES ON UPTAKE, RETENTION AND DISTRIBUTION OF RADIONUCLIDES BY THE FOETUS

1. INTRODUCTION

1.1 Terms of Reference

This review was requested by the Atomic Energy Control Board (AECB) in response to proposed changes to the AEC Regulations (C-83) concerning the dose limits to an embryo or a foetus.

The author was instructed to conduct a comprehensive review of the available scientific literature concerning studies of uptake, retention, and distribution of radionuclides by an embryo or a foetus following maternal intake in order to:

1) facilitate internal dose calculations, and
2) identify areas for further research to improve the accuracy of relevant dosimetric parameters.

1.2 Background Information

The proposed General Amendments to the AEC Regulations (C-83) refer to a dose limit to an embryo or a foetus. This differs from the current practice of limiting exposure to an embryo or a foetus by applying a dose limit to the abdomen of a pregnant woman. In view of the proposed change, it is important to be able to assess the dose received by the embryo or foetus with sufficient accuracy to ensure compliance with the proposed dose limits.

An embryo or a foetus can be exposed to ionizing radiation by external or internal sources. The dose from external sources can be assessed relatively easily by standard dosimetric techniques, while an accurate assessment of the dose from internally deposited radionuclides is more complex. An accurate estimation of the internal dose to an embryo or a foetus depends on a number of biological parameters associated with the uptake, retention, and distribution of different radionuclides under various metabolic conditions in both the mother and the embryo or foetus. Quantitative information on these parameters is quite limited, and more research is needed. This literature review examines the extent to which relevant quantitative information on the various biological parameters pertaining to the dosimetry of an embryo or a foetus is available, and identifies the potential areas for further research to improve the accuracy of these parameters.

1.3 Method and Report Structure

A computer search of the available literature from the last 10 years was conducted and the references obtained were scanned to select those that might have relevant information on radionuclides commonly used by Canadian licensees. Wherever possible, reviews were directed towards obtaining quantitative information on uptake, retention and distribution parameters, and other relevant dosimetric parameters.

The radiation hazards of radioactively tagged organic molecules are not generally considered in this review.

In addition, since the review concentrated on isotopes commonly encountered by Canadian licensees, this review does not include cadmium, cerium, tungsten, plutonium, and most of the actinides and other related heavy elements. However, some pertinent references to these elements are listed in Appendix A.

This report summarizes the methodologies, results and conclusions of the relevant studies, reports and reviews. The major conclusions and recommendations follow the summary of these studies, reports and reviews. The reviewed elements are reported in order of ascending atomic number.

2. REVIEW OF THE LITERATURE

2.1 Methodologies

Material is available for placental transfer to the embryo or the foetus only while it is present in the maternal bloodstream. In a typical experiment, a pregnant animal is exposed to a given radionuclide by an intraperitoneal (I.P.) or by an intravenous (I.V.) injection. A few instances involve ingestion of a particular radionuclide. In order to obtain a temporal pattern of concentration in the maternal and the foetal tissues, the animals are sacrificed at sequential times and maternal, placental and foetal tissues removed and analyzed. Results are usually reported qualitatively or in terms such as "percent injected dose retained", where dose is defined as the amount of any agent (drug or radionuclide) administered at one time.[1] Often, the animal data are extrapolated to man. For purposes of comparison, it might be noted that the stages of major organogenesis and of subsequent foetal growth are roughly from 7 to 13 d and from 14 to 21 d after conception in mice or rats, as compared to roughly 10 to 55 d and 56 to 280 d, respectively, in humans.[2,3]

Most experimental techniques used to determine the kinetics of maternofoetal transfer can only be done in late gestational ages. A few studies have been done to determine the rate of transfer of a radionuclide from the maternal bloodstream to the foetal bloodstream. Rarely is the reverse (foetomaternal transfer) measured. It is not always clear if the injected activity (or dose) is typical of the forms which humans can expect to be exposed to, or if the levels of injected activity are typical of the diagnostic or therapeutic amounts used for humans. In some reports, it is unclear if the author(s) mean injected activity (or dose) or the resulting dose from a given amount of activity. Therefore, to avoid errors of misinterpretation, gestation times and units of radioactivity are presented in the words of the original authors.

Human data is obtained from legal and spontaneous abortions in the first trimester (10-14 weeks), the second (22-24 weeks) and early third (26 weeks) trimester, and from stillbirths. In a very few cases, radionuclides have been administered to consenting women who were having an abortion.

Some data on placental transfer were obtained during the evaluation of high dose effects to an embryo or a foetus. Radiation or chemical toxicity, maternal metabolic differences, and mass effects of the administered element can affect the maternal blood levels, the maternal blood flow to the placenta and the transfer of the element to the conceptus. Routes of administration can also affect the rate of absorption and the temporal pattern of the elemental concentration in the maternal and embryonic or foetal blood. Experimental design also affects the end results.

Interspecies variations are a consideration in many studies. Some variations can be explained by differences in the visceral yolk sac. In rodents, the yolk sac persists throughout gestation and has a tendency to concentrate heavy elements. In higher mammals and in humans, the significance of the yolk sac for concentrating radionuclides is not as great. In animal

experiments, the umbilical cord is not usually analyzed, but it is analyzed in human abortuses. In many instances, the umbilical cord is found to have higher concentrations than those found in the embryo or the foetus, or in the amniotic fluids and membranes. The placenta, umbilical cord, and most of the accompanying sac are, of course, cut off from the embryo or foetus at birth.

It should be noted that the reviewed papers do not generally consider the contribution to foetal dose by irradiation from activity retained in the placenta or in the maternal organs. In the case of high-energy radionuclides, this component of foetal dose could be significant.

2.2 Specific Elements

Wherever possible, reviews were directed towards obtaining quantitative information on uptake, retention and distribution parameters, and on any other relevant dosimetric parameters. In order to avoid errors of misinterpretation, gestation times and units of radioactivity are presented in the words of the original authors. The standard conversion factors which can be used are 1 μCi = 37 kBq and 1 rad = 10 mGy.

There are 19 elements summarized in this report. The reviewed elements are reported in order of ascending atomic number.

2.2.1 Tritium (Z=1)

Tritiated water (HTO) is a radioactive product of nuclear power production. In high concentrations it can affect the life span, central nervous system and reproductive functions of an animal in the same manner as high doses of external radiation. The placenta does not act as a barrier to the tritium oxide.

To study the transfer of tritium oxide from the mother to the embryos, Moskalev, Lyaginskaya and Isotomina[4] administered the isotope (0.3 mCi per g of body weight) by ingestion to rats on the first day of pregnancy. By assuming a water content of 88% for the foetus and of 67% for the mother, they calculated, for this intake, an absorbed dose of 1.02 rad for the maternal body and 1.37 rad for the foetus. Tritium concentrations in the dry foetal tissues were 2 to 3 times lower than that of the mother.

In a maternal oral uptake study[5] in mice, the tritium activity in wet tissues of foetuses increased with prolongation of the drinking period, reaching a maximum after about 200 h and falling with the further prolongation of the period.

For newborn pigs from sows given tritiated water during pregnancy, the foetal relative specific activity (ratio of measured specific activity in a given tissue to the specific activity ingested by the mother) was found to be about 0.7 for body water and about 0.14 for organically bound tritium (tritium left after repeated freeze-drying) in most tissues, with the brain (0.22) being the highest[6].

Ujeno and Takimoto[7] developed a compartment model to describe the transplacental transfer of tritiated water after a single injection into a pregnant female mouse. In this model, activity enters the female and is transferred to the foetus. From the foetus, the activity returns to the female transfer compartment for direct urinary excretion. It is assumed that:

1) the amount of water in the female is constant,
2) the amount of organically bound tritium (OBT) is negligible compared to the amount of tritiated water in the wet tissues of the foetus and of the mother (less than 1%), and
3) isotope effects are negligible.

The resulting model presents a first approximation of the foetal metabolism of tritiated water but does not fit their experimental data well. However, some of the differences can be qualitatively explained by physiological reasoning - for example, by considering the effects of organogenesis. In humans, the model would have to be extended to include a longer gestation period, changes in kidney function of pregnant women and non-negligible levels of OBT.

2.2.2 Phosphorus (Z=15)

In guinea pigs, inorganic phosphate [P_i] is transferred from the mother to an embryo or a foetus against a concentration gradient. This implies that there is an active P_i transfer mechanism. Placental uptake from the mother to the embryo or to the foetus is a carrier-mediated process dependent on extracellular Na^+ and on placental metabolism[8]. A study of the effects of ^{32}P on the developing pituitary gland[9] showed that injection of 1.0 μCi per g body weight to the seven-day pregnant mouse did not influence the pituitary gland of either the foetuses or newborns after birth.

No quantitative dosimetric information was found.

2.2.3 Iron (Z=26)

Performed studies[10,11,12] have shown that due to an active transport mechanism, the placenta does not act as a barrier for maternofoetal iron transfer in rats. Since the foetal requirements for iron increase abruptly at a late stage of gestation, experiments involving radioiron in rats are usually carried out during the last 7 days of gestation. After 2 hours, 45.7% of the injected dose is found in the litter. By the end of the pregnancy, the litter retains nearly 75% of the maternal radioiron dose.

Injection with ^{59}Fe citrate results in foetal rat kidney, liver and blood radioiron levels that are 10 times greater than that of the corresponding maternal levels[11]. When 5 μCi of ^{59}Fe-citrate was administered to the dam, the percentage of the injected dose retained per rat foetus was 1.35, 2.53, 2.61 and 3.27 at 1, 5, 8 and 24 hours post injection[11]. Takahashi et al.[10] injected pregnant rats with ^{59}Fe-dextran, with ^{59}Fe-transferrin or with ^{59}Fe-transferrin and stable iron-dextran. After 4 hours post-injection, foetal activity was higher when ^{59}Fe-transferrin was administered without stable iron-dextran, which competed for the iron reaction sites of the

placenta. When injected as ^{59}Fe-transferrin, foetal ^{59}Fe blood concentrations were stable at 0.018, 0.019 and 0.017% of the injected dose per mL of plasma after 1, 2 and 4 hours. Between 2 to 4 hours after an ^{59}Fe-dextran injection, the foetal accumulation was 0.033% of the injected dose per g of wet weight of foetus. Saturation of placental binding sites with non-radioactive iron drastically decreased embryonic liver radioactivity[10].

2.2.4 Cobalt (Z=27)

Cobalt is transferred across the placenta to the developing rat conceptus[13,14]. The activity of ^{60}Co transferred to the foetus increases with the time of gestation but levels found in the yolk sac are constant throughout gestation. Deposition within the foetus increases by as much as 46 times in the last 6 continuous days of gestation. This increase is accompanied by growth of the foetal body weight in the last 3 days of gestation. The concentration of ^{60}Co per g foetus increases by nearly 3 times just before birth.

This continuous increase in cobalt transfer does not resemble the pattern of retention found in other physiological trace elements[15]. The growing ^{60}Co retention may be due to an increased cobalt transport across the placenta and/or to a growing capacity of the foetal liver and kidney for binding cobalt. It is not known in which form the ^{60}Co is retained.

When Nishimura, Inaba and Ichkawa[14] injected pregnant rats with $^{60}CoCl_2$ or ^{57}Co-cyanocobalamin at various stages of pregnancy, they found that the transplacental transfer of cobalt in the cyanocobalamin form was much greater. Roughly half of the dose is transferred to the foetuses when the pregnant rats are given ^{57}Co-cyanocobalamin at day 20 of the pregnancy.

It should be noted that these papers do not consider the contribution to foetal dose from irradiation due to activity in the placenta or in the maternal organs. In the case of ^{60}Co, this component of foetal dose could be significant.

2.2.5 Nickel (Z=28)

Throughout gestation, nickel crosses the placental barriers to the developing conceptus[15,16]. Nickel is distributed throughout the early embryo, concentrating in the foetal soft tissue, in particular the liver and the kidneys, and in mineralized tissues[17]. Foetal accumulation of ^{63}Ni increases until day 16 of gestation, when the foetal kidney becomes fully differentiated, functional and begins to excrete ^{63}Ni. Foetal levels of ^{63}Ni then drop. Foetal tissue concentrations remain greater than that of the mother.

Olsen and Jonsen[10] found long-term retention of ^{63}Ni in the visceral yolk sac. Because of this long-term retention by the yolk sac, the embryonic/foetal chemical toxicity of nickel may be due to placental accumulation rather than maternal or foetal retention. The additional presence of ^{63}Ni in the amniotic fluid and subsequent drinking of this fluid by the foetus may also contribute to the foetal accumulation.

2.2.6 Zinc (Z=30)

Zinc is one of the essential, readily accumulated, elements in animal nutrition. It is indispensable to a number of physiological processes. Radioactive zinc (^{65}Zn) is produced by neutron activation in many nuclear processes, released to the atmosphere by thermonuclear detonation and incorporated into foodstuffs. It has a relatively long half-life and is readily transferred to the embryo or to the foetus.

Foetal uptake of ^{65}Zn increases with duration of administration and varies with time of gestation at the moment of administration[18,19,20]. When administered on day 18 of gestation, 1% of the dose per g wet weight of foetus was retained by the rat foetus 24 hours post-injection[19]. When injected in pregnant mice on day 17 of gestation, 27% was retained by the litter (about 1.8% of the dose per g wet weight of mouse foetus)[20]. Foetal ^{65}Zn concentrates in blood, liver and kidneys, where it exceeds by more than 2.5 times the levels in the maternal blood and liver. Foetal ^{65}Zn kidney concentrations were less than that of the mother.

From day 15 to day 22 of gestation, foetal uptake of ^{65}Zn increases by more than 25 times[18]. If the foetoplacental unit and the mother are taken as a single entity, then 40-45% of the total burden is accounted for by the litter. In another study, Matsusaka[20] found that, since ^{65}Zn uptake by the mouse foetus is most intense from day 15-19 of gestation, then foetal contamination would be reduced if contamination of the dam occurred prior to this time interval.

Zyliciz[19] found a great similarity between the accumulation of ^{65}Zn and of Fe in foetal tissues and in the yolk sac. This similarity and the presence of zinc in carboanhydrase of erythrocytes suggests that Zn foetal retention is a function of foetal hemopoiesis. Because of the ability of the liver to form blood (14th-16th day), combined with an increase in the liver's weight and ability to bind zinc (15th-19th day), a maximum zinc concentration in the rat foetus is expected on the 19th day. This peak concentration was indeed observed[18,19,20].

2.2.7 Gallium (Z=31)

Radiogallium, ^{67}Ga, is widely used for the detection of malignancies. Animal studies have shown that ^{67}Ga diffuses across the placenta to the foetus. Although human foetal data is obtained by extrapolation to man, clinical studies have shown that the biodistribution of intravenously administered ^{67}Ga-citrate in animals and in adult man is similar[21,22].

The tissue distribution of Ga within the mouse foetus is similar to that of the mother[21], with the highest foetal 24-h uptake being during organogenesis. At day 6 of gestation, scattered labelling is observed. From day 8 to 13, localization is seen in the decidua, the foetal membranes and in the limb buds. Thereafter, ^{67}Ga concentrates in the skeleton and the cartilaginous precursors.

When hamsters were injected with ^{67}Ga on the first day of pregnancy, by day 10 of gestation, 11% of the administered ^{67}Ga was retained by the foetus; this concentration was similar to that of the mammary glands of the dam[20]. At day 14, the concentration of ^{67}Ga dropped to 5% due to the dilution effect of rapid foetal growth. Haynes and Byrd[22] postulated that the most important phase to the radiation hazard to embryonic tissue is in the transfer of ^{67}Ga in the early stages of pregnancy.

Several years earlier, Wegst[23] studied the transplacental transfer of ^{67}Ga in rats and in rabbits. Rats were injected with ^{67}Ga and rabbits were injected with ^{75}Se and ^{67}Ga. Less than 0.1% of the injected dose per gram of foetus was found in the rat and less than 0.02% per gram in the rabbit foetus. Six hours after injection, placental uptake increased from 2.7% per g at day 15 of gestation to 6.8% per g at day 21. Rat uterine concentration was about 1% per g throughout the pregnancy. Wegst stated that if this data can be extrapolated to man, then foetal dose due to activity within the foetus is negligible, and also stated that the foetal dose can be calculated by only considering the contribution due to activity in the material organs and in the placenta. The paper is only available in summary form.

2.2.8 Strontium (Z=38)

Both animal and human studies have shown that strontium concentrates in the skeletal system of the foetus, with the amount being retained by the foetus being greatest when the strontium is administered in late pregnancy at the onset of foetal classification. Total strontium retained has also been shown to be correlated with the increasing weight of the foetal skeleton. However, retention of very small amounts of strontium before the onset of ossification seems to indicate a relationship between retention and foetal skeletal metabolic activity[24,25].

In studies with rats, 0.7% of the injected dose is found in the foetus at parturition when the contamination of the dam is done at day 14 of gestation. When the injection is done on day 18 of gestation, the foetal retention increases to 4.6% at parturition[26].

The injection of 11.1 kBq of ^{90}Sr to the dam, with a corresponding retention of 0.5-0.6 kBq per foetus, results in a decrease in the number of oocytes in the early development stages of the mouse foetus[27,28]. A seriously disturbed reproductive capacity and an increase in the incidence of proliferative events was not noted until 185 kBq or 8.5 kBq per foetus, respectively.

In humans, the variation in the Sr-to-Ca ratio in foetal bone with foetal age remains fairly constant at 0.231 ± 0.025 mg Sr per g Ca. This is less by a factor of 2 than the ratio measured for newborn in Moscow but similar to studies done in Israel[29]. Based on their data from human foetal bone, Kawamura, Tanaka and Shiraishi[30,31] have assumed that the strontium concentration in foetal bone remains constant throughout the second and third trimester of pregnancy.

From fallout measurements during 1957-1966[32], the human foetal to maternal ratio of ^{90}Sr activity concentration is 4. The foetal effective half-life is 21 d for a 6-month foetus and 97 d for a 9-month foetus. Roedler[32] calculated that the 6 month foetus absorbed 65% of the emitted energy and states that the committed dose per MBq intake is 0.22 Gy for the 6-month foetus and 0.67 Gy for the 9-month foetus.

2.2.9 Selenium (Z=34)

Selenium (^{75}Se), incorporated into the amino acid methoionine, crosses the placenta and is widely distributed throughout the foetus[33]. In injection studies on pregnant rats and sheep, foetal concentrations were approximately one half the maternal concentration. When injected on day 11 of pregnancy, rat foetuses contained 1.7% of the injected dose per gram foetus, dropping to 0.6% at 19 d. The absolute amount per foetus increased from 0.05% of the injected dose per foetus at 11 d to 1% at 19 d. In both rats and sheep, foetal tissue concentrations were approximately 50% of the corresponding maternal concentrations.

2.2.10 Krypton (Z=36)

When pregnant ewes were exposed to 50 nCi per mL of ^{85}Kr, equilibrium concentrations in maternal blood and in most tissues was approximately 1 nCi per g[34]. Similar levels were obtained for the foetal lambs, suggesting that ^{85}Kr is transferred across the placenta to the developing conceptus.

2.2.11 Technetium (Z=43)

Technetium pertechnetate readily crosses the placental barrier and is retained by the foetus. Wegst[35] looked at the foetal accumulation of ^{99m}Tc in rats, ranging from 13 to 21 d in gestational age. She found that unlike the maternal organ retention, foetal accumulation was not simply a function of gestational age: it exhibits an increase with time that parallels the gain in foetal weight. Placental accumulation and weight increased linearly with time. She also found that the placental barrier was less effective during the early stages of placental formation and at near term, such that the amount of ^{99m}Tc transferred to the foetoplacental unit varies substantially with time.

In the embryo or foetus, a portion of the ^{99m}Tc appears to be incorporated into biomolecules. It is known that when combined as biomolecules, radionuclides that decay by electron capture or isomeric transition may show a lethality greater than that predicted from the amount of energy released[36].

The nonpenetrating fraction of ^{99m}Tc consists mainly of low-energy conversion electrons and accounts for about 14% of the total emitted energy per decay. The resulting radiation effects from this nonpenetrating fraction are therefore highly dependent on the cellular site at the time of decay.

For a 1.48 MBq injection of ^{99m}Tc in rats, a maximum foetal retention of 6.7 Bq-h per g tissue is seen on day 13 of gestation. At mid-term, foetal

retention activity decreases by a factor of 2.5 and then increases to 5.01 Bq-h per g at term.

To see if animal data for ^{99m}Tc could be used for man, Wegst[35] used the accumulated activities of non-pregnant rats and the available S factors for man for ^{99m}Tc[37]. The calculated absorbed doses were then compared to published data. She then extrapolated these doses to man using the McAfee time equivalent factor[38] to expand the animal time base to man. This factor is based on a weight ratio between man and animal. Published data fell within the range created by these two estimates. She repeated this exercise for the foetus by using the foetal rat data and the available S factor for a 58 kg pregnant woman of 1-2 months gestation[39]. A foetal absorbed-dose estimate of 85.8 mRad per μCi for early pregnancy was obtained. The previously published[40] estimates of 10 mRad per μCi are lower by a factor of almost 9. The whole-body foetal dose to whole-body maternal dose ratio at 2 months gestation is about 5.

2.2.12 Indium (Z=49)

Indium isotopes, such as the widely used ^{113m}In, are preferentially retained by the placenta. After 5 hours post-injection, up to 37% of the administered dose is found in the placenta of rats[41]. Placental retention is highest in the late stages of pregnancy. In comparison, transfer to the foetus is small and does not exceed 1% of the injected dose. The foetal radiation hazard is mostly due to the ionizing radiation from In external to the foetus and is therefore dependent on the placental cellular site at the time of decay.

2.2.13 Iodine (Z=53)

Placental transfer of radioiodine has been extensively studied by several people. It is agreed that iodine taken by the mother is readily transferred to the embryo or foetus. At about 90 d, the human foetal thyroid will start to concentrate iodine.

This initial retention will a have a relatively long half-life. There is large disagreement as to the value of the half-life of iodine retention in the foetal thyroid. On the basis of published data, Johnson[42] claims that this half-life will decrease to 1300 d, 120 d and 70 d at 100, 200 and 270-days of gestation, respectively. This has been disputed by Roedler[32] on the basis of the data from Aboul-Khair et al.[43]. Roedler claims that the effective half-life is 0.58 d, 1.9 d and 4.8 d at 100, 200 and 270-days of foetal age, respectively. Johnson[40] notes that Roedler's half-lives are not consistent with all of the observed data.

Johnson[44] extended the age and stable iodine-dependent model to calculate foetal thyroid doses. The dosimetry calculations included the age dependence of the absorbed energy and thyroid mass and the age dependence of the uptake and retention of iodine in the foetal thyroid. Foetal thyroid doses from unit intakes (ingestion or inhalation) of radioiodine by the mother were calculated to increase sharply from zero at day 90 of gestation, to peak at day 130 of gestation and to steadily decrease to between one third (^{123}I)

and one half (^{129}I) at term. The maximum foetal thyroid doses are about a factor of two above those to the mother's thyroid, whereas Roedler claims that the foetal thyroid doses at 130 d of gestation are one third of those for the mother.

Battin, Hehunstre, Azanza and Sainz[45] reviewed data on the administration of 50 mCi of ^{131}I to consenting women who were having an abortion. Of the retained ^{131}I, 65% is found in the foetal thyroid, 16% in the skeleton and 19% distributed in other organs. It was shown that the foetal thyroid dose increased from 1.3 rads per μCi administered to the mother at week 14 to 6.5 rads per μCi at week 22. Using these numbers, the administration of 50 mCi of ^{131}I to the mother, at week 14 of gestation, would result in a foetal thyroid dose of 650 000 rads.

Generally, the foetal to maternal radioiodine concentration ratio (F/M ratio) exceeds 1 as the pregnancy progresses, increases near parturition and varies with the duration of exposure[46]. In sheep, chronic feeding of radioiodine to the pregnant can give F/M ratios of 2.5. In humans exposed to fallout the F/M ratios varied from 1.3 to about 8[47,48]. No information is available as to when the intake began during the pregnancy but it is implied that this is a chronic intake setting that begins prior to pregnancy and continues to term. By using data on human foetal and maternal uptakes 16-48 hours after an acute intake of ^{131}I to the mother, and by assuming an average maternal uptake of 30% by a 17 g thyroid, F/M ratios of about 1.2, 1.8 and 7.5 were calculated for the 12th-13th weeks of pregnancy, for the second and third trimester, respectively[49].

By assuming 30% thyroidal uptake, a 100 d biological half-life and a 17 g maternal thyroid, Book et al.[50] calculated that a chronic 1 pCi per day maternal intake would produce a steady-state maternal thyroid burden of 2.5 pCi per g thyroid. This results in a maternal thyroid dose rate of 3.0 mrem per year. Book further assumed that the foetus has a near-term concentration 3 times the maternal thyroid burden (7.5 pCi per g thyroid), such that for a 1 pCi chronic maternal intake, the foetal thyroid dose would be about 9 mrem per year. A chronic maternal intake of 1530 pCi ^{129}I would give a foetal thyroid dose rate of 13 rem per year. He calculated that if the maternal thyroid contains 2.5 pCi per g thyroid and 0.6 mg iodine per g thyroid, then the ^{129}I specific activity for the maternal thyroid would be 4.2 pCi ^{129}I per mg iodine. Similarly, a near-term foetal thyroid burden of 7.5 pCi per g thyroid and 0.03 mg iodine per g thyroid gives a foetal thyroid ^{129}I specific activity of 250 pCi ^{129}I per mg iodine. This, he claimed, reflects a more "complete labelling of growing storage pools in the developing thyroid"[50]. Ichikawa[51] refutes this statement. He states that if the maternal thyroidal specific activity is 4.2 pCi ^{129}I per mg iodine, then this is a well-labelled maternal thyroid. As a result, the specific activity of ^{129}I in the foetal thyroid should be the same as that of the mother. Ichikawa suggests that the amount of stable iodine in the foetal thyroid was considerably underestimated by Book.

In animal studies involving guinea pigs, the disappearance of ^{131}I from the foetal blood had two components: a short component of 0.3-6 d, and a long component of 6-7 d[49,52]. Peak concentrations of 200% injected dose per g were

seen at 3 d post-injection, with foetal thyroid doses estimated at 90 rads per μCi injected. The ^{131}I concentration of the maternal and foetal carcasses decrease from 54 and 253% of the injected dose per kg carcass, respectively, 2 and 7% per kg carcass at 9 d.

Book, Wolf, Ishizaki and Parker[53] studied the exchange of iodide between maternal and foetal blood and between foetal blood and amniotic fluid. They injected ^{131}I into the ewe and ^{125}I into the foetus or the amniotic fluid. Regardless of the injection site, after 48 hours, iodide concentrations were greatest in the amniotic fluid, followed by foetal thyroid and maternal blood. Foetal to maternal radioiodine per g thyroid ratios of 4.8, 6.2 and 21 were obtained after injection into the ewe, into the foetus and into the amniotic fluid, respectively.

Canning and her group[54] studied the radioiodide transfer across sheep placenta by measuring, among other things, the unidirectional and bidirectional clearance of radioiodine. She found that steady-state conditions were obtained 20 minutes after injection of a ^{125}INa or ^{131}INa bolus. The foetomaternal unidirectional clearance rate of 11.1 $\pm$ 1.0 mL of plasma per minute did not correlate with gestational age or foetal weight or the potential difference across the placenta. Maternofoetal unidirectional clearance rates of 10.9 $\pm$ 1.9 mL of plasma per minute slightly correlated with the potential difference across the placenta. Bi-directional maternofoetal to foetomaternal plasma clearance ratios ranged from 0.75 to 1.26.

2.2.14 Cesium (Z=55)

Cesium is easily transferred from the mother to the embryo or foetus, where it is uniformly distributed. There is currently no available data as to the effective half-life of ^{137}Cs within the human foetus. Roedler[32] assumed that it was the same as for the mother (50 d). Roedler[32] also states that for humans, the foetal to maternal activity concentration ratio is about 1, that the foetal to maternal whole-body dose ratio is about 1 and that the foetal to reference man whole-body dose ratio is about 0.5.

2.2.15 Gold (Z=79)

The placenta is impervious to colloidal radioactive gold. Within 15 minutes of an ^{198}Au injection into the ileac vein of pregnant rats, more than 90% of the injected ^{198}Au is found in the maternal liver, with no observed transfer to, or accumulation by, the foetus[55]. This reference reports the technique developed for the intrafoetal administration of radiogold in order to directly affect the foetal liver and the erythropoetic process. No mention is given to the foetal dose due to the retention of ^{198}Au by the maternal liver.

2.2.16 Thallium (Z=81)

Throughout gestation, thallium will cross the placenta. Both maternal and foetal organs will show considerable thallium retention, with approximately 10% of the dose still retained 8 days after injection.[50] Four hours after a 2 μg I.P. injection of ^{201}Tl-thallium in the rat on day 13 of

gestation, Rade et al.[56] found that 1.4 ng of ^{201}Tl was in the foetal liver and 0.8 ng in the foetal brain, with the average foetal brain to maternal brain ratio being 0.9. By autoradiography, Olsen and Jonsen[57] qualitatively examined the foetal Tl distribution. Their findings confirm those of Rade and his group, that throughout gestation, ^{201}Tl concentrates in the decidua of the early embryo, and in the kidneys, skeleton brain and eyes of the late foetus.

It has been suggested that the higher (with respect to the mother) foetal uptake and faster removal rate of ^{201}Tl levels in the foetal brain is due to reduced activity mechanisms of ion movement regulation, to the composition of the nervous tissue and the immaturity of the blood-brain barrier in the developing foetal brain[57].

2.2.17 Thorium (Z=90)

Foetal concentrations of thorium are dependent on the stage of gestation. Weiner, McInroy and Wegst[58] determined the levels of environmental thorium in human foetal tissue. Samples were taken from legal abortions in the first trimester (10-14 weeks) or, second (22-24 weeks) and early third (26 weeks) trimester. Detectable amounts of ^{230}Th were found in five of the seven first trimester samples. Unfortunately, this paper is only available in summary form. However, it does show that Th is transported across the placental barrier to the foetus.

2.2.18 Uranium (Z=92)

Uranium is transported across the placental barrier and deposited in the foetus.

Sikov and Rommerein[59] injected 1.8, 3.3, 5.75 or 10 μCi per kg of ^{233}U-citrate into rats at day 9, 15 or 19 of gestation. Exposures at day 9 and 15 produced dose-dependent effects on foetal lethality, on foetal and placental weight and on malformation incidence. Retention by the foetus increased with the increase in dosage but this mass effect was not observed when the animals were at times less than 10 days post-exposure.

Weiner and his group[58] found significant amounts of ^{234}U (1.6 dpm per kg) in 3 out of 7 human abortuses. In the second- and third-trimester samples, 12 out of 16 showed high foetal levels of ^{234}U, with values ranging from 0.097 to 0.32 dpm per kg. No U concentration effects were observed in the foetus, since a reference female contains 2.1 dpm per kg of U.

2.2.19 Americium (Z=95)

There is a low placental transfer of ^{241}Am to the foetus. While looking at the comparative effects of prenatal exposure of ^{241}Am with those of ^{239}Pu, Sikov[60] found that the embryotoxic effects of ^{241}Am on rats were similar to those of ^{239}Pu, but were quantitatively less when based on administered dose. These results were confirmed by Weiss, Walburg and McDowell[61].

When injected at day 9 of gestation, the rat embryo had a concentration of 0.002% of the injected dose per g on day 12 of gestation. This decreased

by a factor of two or three by day 20. Injection at day 15 gave foetal levels of 0.001-0.002% dose per g after one and five days. Injection at day 19 yielded concentrations of 0.23% dose per g. Autoradiographic investigations[62] estimate foetal rat concentrations of 0.0015% of the injected dose per g, and 0.15% of the injected dose per g, respectively, after injection at day 15 and 18 of gestation, with most of the ^{241}Am activity found in the foetal membranes and in the foetal liver and skeleton.

Weiner et al.[58] were unable to detect ^{241}Am in first-trimester human foetuses. Six of the second-trimester samples showed levels of ^{241}Am ranging from 0.08-0.29 dpm per kg. Umbilical-cord values from 1.0 to 2.1 dpm per kg were observed.

3. CONCLUSIONS

From the animal studies and the limited human data, it is evident that after maternal contamination, the embryo or the foetus accumulates and retains most radionuclides. Unfortunately, very little human data is available and a large fraction of the quoted values of human foetal dose retention are obtained from extrapolation from animal experiments.

The information obtained in animal experiments is useful in determining general patterns of retention and distribution of radionuclides within the foetoplacental unit. These trends and retention patterns cannot always be completely correlated with the very limited human foetal data available. Biological distribution data as a function of gestational age should be acquired for many of the radionuclides reviewed in this work, and possibly some radiopharmaceuticals. This data would allow for a better understanding of the risk for occupationally exposed individuals.

It may also be useful to extend the features of Johnson's foetal iodine model[44] to other radionuclides. The resulting foetal dosimetry calculations would include age dependence of the absorbed energy and the foetal organ masses, as well as age dependence of the uptake and retention of various radionuclides in foetal organs.

In addition, whenever human foetal data becomes available, it should be incorporated into existing data banks and dosimetry models.

4. RECOMMENDATIONS

It is recommended that:

1) Whenever possible, further human data on the uptake, retention and distribution of radionuclides by the embryo or the foetus should be obtained, in order to improve the accuracy of relevant dosimetric parameters.

2) Foetal models for the most commonly used isotopes by Canadian licensees, specifically HTO, C-14, I, Tc-99 and U, should be re-examined and further developed in order to allow for a better understanding of the risk to the foetus from occupationally exposed individuals. For the iodines, this will require resolving the disagreement as to the value of the half-life of foetal iodine retention.

3) The foetal iodine model developed by Johnson[44] should serve as a guide for other radionuclides. Foetal dosimetry calculations should include age dependence of the absorbed energy and the foetal organ masses, as well as age dependence of the uptake and retention of various radionuclides in foetal organs.

4) The HTO model proposed by Ujeno and Takimoto[7] should be extended to include longer gestation periods and non-negligle amounts of OBT.

5) The feasibility of applying the McAfee equivalent when animal data is extrapolated to man should be examined.

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APPENDIX

This review concentrates on isotopes commonly encountered by Canadian licencees. It does not include elements such as cadmium, cerium, tungsten, plutonium, and most of the actinides and other related heavy metals. For convenience, the following is a list of some of the pertinent references to these elements.

Cadmium (Z=48)

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Tungsten (Z=74)

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