EXECUTIVE SUMMARY OF FINAL REPORT

Contract no.: FIGD-CT2000-00053 — **BIODOS**
Title: **Biokinetics and Dosimetry of Internal Contamination**

Introduction

Assessments of doses and risks to workers and to the public exposed to radionuclides require biokinetic models which describe the behaviour of the radionuclides from their entry into the body until their final elimination and dosimetric models for calculating doses within tissues. Biokinetic models describing the absorption of radionuclides after ingestion or inhalation and subsequent systemic behaviour, published by the International Commission on Radiological Protection (ICRP), are widely used in dose calculations but are subject to revision as knowledge improves.

- The ICRP Publication 30 (1979) gastrointestinal (GI) model was developed specifically to calculate doses to workers, either from the direct ingestion of radionuclides or following their inhalation as particles with subsequent clearance from the lungs to the alimentary tract. Since the publication of this model, a considerable body of data has become available on the transit of materials through the different regions of the gut that include data on differences between solid and liquid phases, age- and gender- related differences and the effect of disease conditions. These data may be used to determine default transit rates for the age-groups given in ICRP Publication 56 that is, 3 month-old infants, 1, 5, 10 and 15 year-old children, and adults. In addition, the 1990 recommendations of ICRP introduced specific risk estimates and tissue weighting factors, w_T, for radiation-induced cancer of the oesophagus, stomach and colon, requiring dose estimates for each of these regions. The Publication 30 model did not include the oesophagus and treated the colon as two regions – upper and lower large intestine. The Publication 30 model also made simplifying assumptions in the calculation of doses to GI tract regions from non-penetrating radiations from radionuclides in transit and took no account of possible retention of radionuclides in intestinal tissues or possible absorption in regions other than the small intestine. It was considered therefore that there is a need to develop a new age-dependent model that would take account of these factors and provide estimates of doses to all regions of the alimentary tract.

- Age-specific biokinetic models are given by ICRP for 31 elements. For these elements, dose coefficients were calculated for the most radiologically significant natural or artificial radioisotopes that might be released into the environment due to various human activities. For a number of important elements and their radioisotopes, new dynamic and physiologically realistic models were developed for the calculation of doses to members of the public. Such models are also applicable to occupational exposures and the interpretation of bioassay data, and there is a need for the development of improved models for a number of other elements (eg. ^{3}H as tritiated water, sulphur, cobalt). An important development in the improvement of dosimetric models is the availability of computed tomographic data which can be used to develop voxel phantoms of the body and organ topology to replace the mathematical representations that are used currently.

- The ingestion of radionuclides in breast milk following intakes by the mother, either from occupational or environmental exposure, is a potential source of radiation dose to the infant. ICRP Publication 88 (2001) gave dose coefficients for the offspring (embryo, foetus and newborn child) of female members of the public and female workers following intakes of radionuclides either before or during pregnancy. To take account of doses from the transfer of radionulcides in breast milk, the development of new models was required.

- Assessment of the radiation doses, and hence risks, associated with exposure to airborne radionuclides requires quantitative information on the deposition of inhaled material in each region of the human respiratory tract and on the pathways of clearance. The ICRP (1994) Human Respiratory Tract Model for Radiological Protection (HRTM) has been applied to calculate inhalation dose coefficients for workers and the public which were adopted in the 1996 Euratom Directive. However, it is recognised that important uncertainties exist in some of the assumptions made in the HRTM, in the 'reference values' of many parameters and in how parameter values vary between individuals. For example, the reference values chosen for the HRTM relating to the subject are intended to be typical representative values for the general population, but are single values based on data for healthy non-smokers. There is a lack of information on how smoking and lung disease affect regional deposition in, and particle transport from, the bronchiolar and alveolar regions. Clearance of radionuclides from the lungs by absorption to blood depends upon the chemical and physical form of the deposited material and this is not addressed explicitly in the HRTM. The model assumes that absorption rates are the same from all regions of the respiratory tract, except for the front of the nose, where it assumes no absorption takes place. It is recognised that this is an oversimplification, but that there is insufficient information available to specify different rates for different regions. Finally, major uncertainties remain in the kinetics of particle transport from the lungs, their underlying mechanisms, and factors affecting them. In particular, the HRTM includes a slow phase of particle clearance from the bronchial tree, which is assumed to depend on the particle physical size but to be the same in all airways. Both assumptions are debated, and the mechanisms involved are unknown. The issue can have a significant impact on effective doses and remains controversial. In summary, the HRTM is fairly robust but the need for improvements is recognised.

Objectives

The overall objective was to improve the scientific basis of existing biokinetic and dosimetric models and to provide new and improved models. The work comprised two parts focused respectively on the delivery of new systemic, alimentary tract and breast-milk models, and on improvement of the HRTM. It combined established experimental and mathematical modelling expertise, including human, animal and *in vitro* studies. The work was divided into 9 work packages (WPs). WPs 1 and 5 were designed to provide new data for inclusion in the models whereas the others were aimed at developing the models described above.

WP 1 aimed to provide experimental data for model development. Human volunteer studies were performed on the biokinetics of Mo, Co, Zr, and Ru. Studies using genetically altered mice investigated the effect of radiation quality on intestinal tumour induction. Additional studies were performed *in vitro* to assess both speciation of U and Cs in the GI tract and deposition of energy in cells from short-range emitters.

WP 2-4 aimed to produce new physiologically-based models and dosimetric methods. Efforts were focused on describing the behaviour of radionuclides after entry in the alimentary tract, transfer to systemic compartments and then to breast-milk. The objectives were to produce age- and sex-dependant dosimetric models and consider the effect of uncertainties in the model parameters on the resulting doses.

WP 5 aimed at examining the importance of heterogeneous distribution of dose within tissues and cells. Two particular configurations of non-uniform exposure relevant to radiation protection were investigated, i.e. radon progeny in epithelial cells of bronchial airways and Auger emitters in cellular systems.

WP 6-9 aimed at improving the HRTM. Studies focused on deposition and particle transport of ultrafine particles (UFP) in the human respiratory tract, inter-subject variation amongst healthy people and patients with lung diseases, determination of factors that affect the clearance of radionuclides from the lungs by absorption to blood and mechanisms of clearance of inhaled particles from the different regions of the human respiratory tract.

Results

The main outputs of BIODOS are a new human alimentary tract model, models for the transfer of radionuclides in breast-milk, development of systemic models, development of voxel phantoms for photon dosimetry, and delivery of new data for improvement of the HRTM. In addition, new data have been obtained for model development and for assessment of the distribution of doses within tissues and cells. This summary concentrates on the completion of new biokinetic and dosimetric models. The interested reader is encouraged to refer to later sections of the report and publications for details of the experimental results obtained.

A new alimentary tract model

A new physiologically based model has been developed, applicable to intakes of radionuclides in food and liquids by children and adults. All parts of the alimentary tract are included and doses are calculated for the oral cavity, oesophagus, stomach, small intestine, right colon, left colon and rectosigmoid (including the rectum). New morphometric and transit parameter values are given that are gender-dependent for adults and are consistent with ICRP Reference Man revisions. Transit times are given for food and liquids, as well as for total diet, for the mouth, oesophagus and stomach.

Calculation of absorbed fractions for penetrating γ radiation is performed with phantoms (see below). An important development in the new model is the calculation of energy dependent absorbed fractions for non-penetrating radiations from radionuclides in transit through the different regions of the alimentary tract. Calculation of dose is made to epithelial target regions within the lining of the alimentary tract. The sensitive cells are assumed to be in the basal layer at varying cell depths in different parts of the mouth and oesophagus. In the glandular epithelium of the stomach, the stem cells are considered to be confined to a band a few cells deep within gastric pits, at a depth from the luminal surface of about one-third of the total depth of the gastric pits. In the small intestine, stem cells are known to occupy positions adjacent to paneth cells in the base of the crypts. Similarly, stem cells in the epithelium of the large intestine occur at the base of the crypts (paneth cells are absent in the large intestine). The results show that for electrons with energies of greater than 0.5 MeV absorbed fractions are insensitive to the assumed depths of target cells. However, the absorbed fractions for lower energy electrons can fall to zero when considering, for example, the 280-300 μm target depth assumed for the colon. These results on dose are given with a brief overview of variability and uncertainties in dose calculation.

Various sites for absorption to blood and retention in intestinal tissues are considered. The default assumption, in the absence of specific information, is that total fractional absorption to blood, f_A, of an element and its radioisotopes occurs in the small intestine, i.e. $f_{SI} = f_A$. Examples are given of the effect on doses of considering retention of ^{115}Cd on teeth and the retention of U and Fe isotopes in the intestinal wall. Work also included sensitivity and uncertainty analyses.

This work has provided substantial input to an ICRP report that has been posted on the ICRP web-site for comment and will be published during 2005. This has involved collaboration between BIODOS laboratories (IRSN, BfS, NRPB) and others, particularly Oak Ridge National Laboratory (ORNL), Tennessee.

A new milk model

The development of milk models was based on reviews of published human and animal data. The quality of data was variable; in some cases (e.g. Ca, Cs and I) good human data were available, while in other cases reliance was placed on animal data (e.g. Pu) or chemical analogy (e.g. Ra). An important input was a compilation of many data derived from German measurements of element-specific intake rates and concentration in milk.

Human and animal data on elemental and radionuclide transfer to milk were used to extend ICRP biokinetic models for adults to include transfer to breast and milk for 35 elements, including H, C, S, P, Fe, Cs, Sr, I, Pb, Pu, Np, Am and Cm. Doses to the infant were calculated for intakes by the mother by ingestion or inhalation at various times before or during pregnancy and during lactation. Acute and chronic intakes were considered. In some cases, changes to the adult models were made to take account of physiological changes occurring during pregnancy and lactation (e.g. Ca and Fe). Milk consumption by the infant was taken to remain at a constant 800 ml d^{-1} until 6 months of age, following an increase from zero over the first week of life.

The transfer of radionuclides to breast milk predicted by the models for single acute intakes during pregnancy or lactation varies substantially from element to element. Expressed as a proportion of activity reaching blood, estimated maximum transfer for intakes at one week after birth ranges from about 50% for ^{45}Ca, 40% for ^{60}Co and about 20-30% for ^{3}H (as HTO or OBT), ^{14}C, ^{75}Se, ^{90}Sr, ^{110m}Ag and ^{131}I, to around 1% or less for ^{42}K, ^{59}Fe, ^{95}Nb, ^{99}Mo and ^{127m}Te. Considering intakes by ingestion, the highest values for transfer to milk, as a proportion of ingested amounts, are about 30% for ^{3}H (as HTO or OBT), ^{14}C and ^{131}I, and about 20% for ^{137}Cs and ^{45}Ca. For a number of radionuclides, the transfer of radioactive decay products to milk contributes significantly to the dose to the infant, with substantial differences in their contribution according to the time of intake relative to the start of lactation. Sensitivity analysis was performed for the models describing transfer of ^{45}Ca, ^{75}Se and ^{79}Se to mothers' milk. Comparisons of dose to the infant from ingestion of milk with corresponding dose to the reference adult show that in most cases the infant dose is a small fraction of the adult dose. It is only in the cases of HTO, ^{45}Ca, ^{75}Se and ^{131}I that infant doses may exceed adult doses, for maximum transfer occurring after maternal intakes by ingestion shortly after birth (ratios of 1.2, 3.1, 1.4 and 2.5, respectively).

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New biokinetic models

An objective of the work was to update and develop biokinetic models required for the computation of realistic radiation doses to the organs and tissues of the human body following intakes of radionuclides of the elements H, C, S, Co, Fe, Zr, Nb, Tc, Ru, I, Ce, Cs, Sr, Pu as well as some other lanthanide and actinide elements. The new biokinetic models developed were to be designed, so far as this was practicable, to enable them to be used for the interpretation of bioassay data as well as for calculation of dose coefficients.

Special attention was paid to H, C and S with a view to identifying which compounds are of sufficient radiological importance for radiation protection purposes to require the development of compound-specific models that could be applied to both prospective and retrospective dosimetry.

Following an extensive re-evaluation of the published information on the long-term retention of tritium, ^{3}H, in the human body, an improved three-component exponential biokinetic model was developed to describe the behaviour of ^{3}H in the human body following an intake of tritiated water (HTO). This model for HTO assumes that 99% of the radioactivity is uniformly distributed throughout the body water and eliminated with a biological half-time of 10 days; 0.98% is incorporated into organic compounds and removed with a biological half-time of 40 days and 0.02% is incorporated into long-lived tissue components and removed with a biological half-time of 350 days. Models for other radionuclides are discussed in the full report.

New dosimetric phantoms of the human body

Extensive calculations of Specific Absorbed Fractions for monoenergetic photon sources were performed using a Monte Carlo photon transport code together with seven male and female adult voxel models based on computed tomographic data of real persons. These models offer greater realism with respect to organ topology than the mathematical phantoms currently used. All these models except Voxelman, were constructed at GSF. The GSF female voxel models are the first voxel models of adult females available. These models are more realistic than the stylised MIRD-type models and furthermore present anatomic variability between themselves, particularly concerning their masses.

The SAFs for organ self-absorption depend strongly on the mass of the organ. If the organ masses are adjusted to a reference value, individual variability of the resulting dose quantity is eliminated, when source and target organ are the same. In many cases, organ cross-fire SAFs can differ by several orders of magnitude for low photon energies between the individual voxel models. However, the larger discrepancies are observed between the voxel models and the MIRD-type mathematical models and the main reason for these systematic differences is an over-simplification of the organ geometry of the mathematical phantoms that cannot realistically replicate the complicated geometry of closely assembled organs.

Improvement of the Human Respiratory Tract Model

Deposition and transport of ultra fine particles (UFP)

The first part of the work included: development of production and inhalation techniques for radio-labelled UFP; measurement of regional deposition and clearance in the human respiratory tract; and modelling regional and local deposition of UFP aerosols.

A commercial ‘Technegas’ generator was modified to produce ^{99m}Tc- and ^{111}In-labelled carbon UFP for human inhalation studies. At KI/SSI, lung retention of inhaled ^{99m}Tc-labelled 100-nm particles was measured for 4 days. Deposition fractions averaged 32% in 6 healthy subjects, 48% in 6 asthmatics, and 56% in 4 smokers. At GSF/Inamed, regional deposition and clearance of UFP (45- and 100-nm) were measured using the aerosol bolus technique (a small volume of aerosol administered at a selected point in the breathing cycle). The tracheo-bronchial (TB) airways were targeted by shallow (end of

breath) boluses and the alveolar (AI) region by deep boluses. Studies were conducted on healthy non-smokers, asymptomatic smokers and patients with mild chronic obstructive bronchitis (COPD). From the regional deposition and clearance data it was concluded that: (1) in the TB only about 20% of deposited UFP are removed within 24 hours by mucociliary action; the rest is retained for the long term; (2) there is no clearance of UFP from AI within 24–48 hours; and (3) translocation of carbon UFP into the blood is low (< 1 %).

Deposition of UFP (1-100 nm) was simulated by a stochastic model using Monte Carlo methods. The results indicate that the alveolar deposition efficiency of all UFP (1-100 nm) is ~ 50 % for sitting breathing conditions. Deposition is not sensitive to the direction of the alveolus orifice relative to gravity, in contrast to particles >1-μm diameter. UFP deposition in bronchial airway bifurcations was modelled numerically. The inspiratory deposition efficiency in a physiologically realistic model approximating the airway generation 3-4 junction, was computed for different particle sizes (1–500 nm), under three flow conditions representing resting to heavy exercise. For the smallest sizes (1–10 nm), molecular diffusion is usually the primary deposition mechanism. For larger particle sizes convective diffusion dominates.

Inter-subject variation (ISV) amongst healthy people and patients with lung diseases
The second part comprised studies of lung morphometry, ventilation, particle deposition in, and clearance from the lungs. Airway calibre and ventilation were measured in 52 healthy non-smokers, 52 asymptomatic smokers, 30 COPD patients without lung emphysema, and 31 COPD patients with emphysema. Airway dimensions were similar in all groups except COPD patients with emphysema, in whom they were much larger. Deposition of shallow aerosol boluses is higher in the left lung than in the right. Experimental data obtained here demonstrate that the asymmetry is caused by ventilation, not deposition. This phenomenon was modelled for healthy people and patients with different lung diseases. Deposition was measured in 13 COPD patients (with lung emphysema) as a function of particle size (1-4 μm), inhalation volume and flow rate. Variation was very large (20-90 %) during normal breathing, but much less during controlled breathing. Complementary modelling indicated that asymmetry and asynchrony affect deposition in individual lobes even under normal conditions, and that non-uniform ventilation plays a minor role in healthy subjects, but may have important effects on deposition in subjects with lung disease.

A stochastic lung model was applied to calculate particle deposition in healthy people of different ages. AI deposition of ultra fine particles (UFP) is higher for 5-year-old children and the elderly than for adults, while for large particles (1–10 μm), the opposite trend occurs. TB deposition has similar tendencies. Extrathoracic (ET) deposition is very similar for adult males, females and children for large particles (1–10 μm) but for UFP deposition is significantly less for children than for adults. Hence AI deposition is significantly higher in children. Deposition in obstructive airways can be significantly different from the healthy case. Disease-specific models were developed for particle deposition in lungs affected by COPD, asthma, chronic bronchitis and emphysema. Deposition patterns in healthy and diseased human airways were analysed by computational fluid particle dynamics (CFPD) methods. In summary: airway narrowing increases deposition for both large and small particles, but more so for small particles. A tumour, even a small one, dramatically increases the deposition efficiency, but only for fine particles. To validate the particle deposition models developed here, predicted total and regional deposition fractions were compared to experimental data, either from this project or the literature. Consistent with the experimental data, predicted AI deposition was lower in patients with emphysema than in normal lungs, while TB deposition was higher in COPD patients, asthmatics and CB patients.

Several experiments were carried out by KI/SSI using 6-μm aerodynamic diameter d_{ae} particles inhaled extremely slowly, to study clearance from small (bronchiolar) airways. Retention of ^{111}In-labelled Teflon particles was followed for about 3 weeks. In 8 pairs of smoking-discordant twins, bronchiolar clearance was somewhat slower in smokers. In 46 healthy subjects with a wide age range (19-81 years, mean 42 years), bronchiolar clearance was slower in the oldest subjects. In 9 CB patients bronchiolar clearance was slower than in healthy subjects. In 6 subjects with immotile cilia syndrome, (ICS), there was significant small airway clearance despite non-functional cilia, indicating that other clearance mechanisms apply. At GSF/Inamed TB retention was measured up to 48 hours in 39 healthy subjects and 23 COPD patients, using shallow aerosol boluses of radio labelled iron oxide particles. Retention was approximated by a double exponential function. The half-time of the fast clearance component in patients was nearly twice that in healthy subjects. The slow-cleared particle fraction and the half-time of the slow component were similar in the two groups.

This work has provided new information on ISV among healthy people and the effects of lung disease on lung deposition and clearance parameter values, particularly those relating to slow particle clearance from the bronchial tree. The implications for doses depend on the decay characteristics and biokinetic behaviour of the inhaled radionuclides. Sensitivity analyses were therefore carried out for six radionuclides with a wide range of decay characteristics, for two aerosol sizes and all three default absorption types: fast (F) moderate (M) and slow (S). The end-points were committed equivalent lung dose and effective dose. It was confirmed that for Type F aerosols ISV in the parameters studied had little effect on doses. However, for Type M or S aerosols they can give rise to substantial differences from those assessed using the HRTM reference values. For example, ISV in regional lung deposition led to ISV in doses of up to about 50%. ISV and the effect of lung disease on slow clearance from the bronchial (BB) and bronchiolar (bb) regions led to variations in doses of up to about a factor of two. The results illustrate the importance of slow TB clearance in evaluating inhalation dose coefficients, and the continuing need to resolve uncertainties relating to it.

Factors affecting clearance by absorption to blood

In the third part of the work the effects of specific surface area (SSA) of uranium and gadolinium particles, and regional deposition, were investigated. Results show that particle size, SSA and composition of the aerosol influence the dissolution and should be known accurately. In the nuclear industries, where many different uranium compounds can be produced, for example, UO_3, UO_4, U_3O_8, UO_2, $U_2O_7(NH_4)_2$, it is likely that mixtures of compounds can be inhaled. The biokinetic behaviour of such mixtures cannot be predicted easily and it is necessary to know at least the particle size to calculate deposition in the respiratory tract, and the dissolution characteristics to assess potential nephrotoxicity. Other experiments involved the assessment of absorption of ^{238}Pu, ^{241}Am, ^{153}Gd, ^{233}U and ^{137}Cs after instillation as citrates into the ET, TB and AI regions of the respiratory tract of rats. The aim of the study was to test whether absorption to blood is the same throughout the respiratory tract, as assumed in the HRTM, or if there are regional differences. The results suggest that absorption is considerably slower from the ET region than from the TB and AI regions.

Improved understanding of lung clearance mechanisms

The fourth part of the work included studies of the role of alveolar macrophages (AM), mucociliary clearance (LMC) mechanisms and modeling of particle transport in the human bronchial tree.

AM were studied in terms of phagocytosis capacity and intracellular (intraphagolysosomal) particle dissolution (IPD). Human AM obtained by lung lavage were loaded with small amounts of carbon UFP in the range 0.02-3.3 $\mu g/10^6$ AM. There was a dose-related decrease in phagocytosis of inorganic test particles (silica). IPD of uniform cobalt oxide particles and phagolysosomal pH (PLpH) were studied in AM from dogs and rats. Co-culturing AM with ultra fine TiO_2 and carbon particles resulted

in a significantly increased IPD rate, but did not show the previously observed correlation between IPD increase and corresponding PLpH decrease. This suggests additional defence processes in the phagolysosome of AM being triggered by UFP, which have an impact on the modulation of the defence against UFP.

In the HRTM it is assumed that the slow-cleared fraction of TB clearance (A-value) decreases with particle geometric diameter (d_p) because the results then available (1994) showed a closer correlation of A with d_p than with particle aerodynamic diameter (d_{ae}). Three subjects inhaled shallow boluses containing 5-µm (d_{ae}) ^{198}Au-labelled gold particles (d_p 1.2 µm) and ^{111}In-labelled polystyrene particles (d_p 5 µm). In each subject, lung retention of the two types of particle was very similar, which is inconsistent with the HRTM. If the findings are confirmed, then consideration should be given to revision of the HRTM assumptions. The long term clearance of magnetic iron oxide particles and investigation of phagocytosis of the particles by airway macrophages were studied in asymptomatic smokers and patients with COPD. Phagocytosis efficiency is lower in the airways than in the alveoli, supporting the assumption that airway macrophages engulf long-term retained particles, but to a lesser extent than alveolar macrophages. Healthy non-smokers showed two phases of particle clearance in the airways after shallow bolus inhalation, with half times of 3 hours (50%) and 109 days. The long-term phase resembles clearance of similar particles from the airways. Despite a larger variation in 24-hour retention of particles in the airways after shallow bolus inhalation, there was no difference between smokers and COPD patients. It appears that a retarded mucociliary clearance in these subjects is compensated by an increased frequency of coughing.

The last part of the work involved the modelling of particle transport in the human bronchial tree. A mucociliary and long-term clearance model of particles being deposited in the airways was developed. A first step was to model particle transport on airway bifurcations and to generate specific transit times. New mechanisms were included in the airway clearance model, such as holes in the mucus blanket, and uptake of particles by airway macrophages, to describe the observed long-term clearance in the airways. The model was adjusted with experimental data, from both the literature and this project. Special efforts were taken to model pathophysiological clearance conditions such as COPD.

Implications

In conclusion, BIODOS has provided substantial input to the development of a new biokinetic and dosimetric model of the human alimentary tract, and models for the transfer of radionuclides in breast milk, together with dose coefficients for infants consuming milk following radionuclide intake by the mother. ICRP reports have been prepared in both cases and will be published during 2005. Another important development is the provision of voxel phantoms of the body and its organs based on computed tomographic data. These more realistic phantoms will replace mathematical phantoms in future ICRP calculations of photon doses. It also provided new data that could be used in the future for improvement of the existing Human Respiratory Tract Model. Experimental studies have provided data that underpin the development of biokinetic and dosimetric models. Overall, BIODOS has successfully contributed to improvements in dose assessments for radionuclide exposures of workers and members of public and therefore contributed to the improvement of radiation protection.

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