RELIABILITY OF THE ICRP'S DOSE COEFFICIENTS

BASIS OF THE HUMAN ALIMENTARY TRACT MODEL AND UNCERTAINTIES IN MODEL PREDICTIONS

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The work of the first author in the preparation of this paper was supported by Contract WF6970Y1 with the U.S. Nuclear Regulatory Commission, Office of Nuclear Regulatory Research, Division of System Analysis and Regulatory Effectiveness (Dr. Robert A. Meck, Project Officer) through Interagency Agreement 41W6970Y1 with the U.S. Department of Energy (DOE).

ABSTRACT

The biokinetic and dosimetric model of the gastrointestinal (GI) tract applied in current documents of the International Commission on Radiological Protection (ICRP) was developed in the mid-1960s. The model was based on features of a reference adult male and was first used by the ICRP in Publication 30, Limits for Intakes of Radionuclides by Workers (Part 1, 1979). In the late 1990s an ICRP task group was appointed to develop a biokinetic and dosimetric model of the alimentary tract that reflects updated information and addresses current needs in radiation protection. The new age- and gender-specific model, called the Human Alimentary Tract Model (HATM), has been completed and will replace the GI model of Publication 30 in upcoming ICRP documents. This paper discusses the basis for the structure and parameter values of the HATM, summarizes the uncertainties associated with selected features and types of predictions of the HATM, and examines the sensitivity of dose estimates to those uncertainties for selected radionuclides. Emphasis is on generic biokinetic features of the HATM, particularly transit times through the lumen of the alimentary tract, but key dosimetric features of the model are outlined, and the sensitivity of tissue dose estimates to uncertainties in dosimetric as well as biokinetic features of the HATM are examined for selected radionuclides.

1. INTRODUCTION

The biokinetic and dosimetric model of the gastrointestinal (GI) tract applied in current documents of the International Commission on Radiological Protection (ICRP) is based on a GI transit model developed by I. S. Eve in the mid-1960s (Eve, 1966). The model was first used by the ICRP in Publication 30, Limits for Intakes of Radionuclides by Workers (ICRP, 1979), and is referred to here as the Pub30 model.

The Pub30 model (Figure 1) divides the GI tract into four segments: stomach (St), small intestine (SI), upper large intestine (ULI), and lower large intestine (LLI), and depicts first-order transfer of material from one segment to the next at rates estimated for a typical adult representing a worker. Absorption of ingested activity to blood is assumed to occur in SI and is described by an element-specific "f_1 value" representing fractional absorption of the stable element to blood. For dosimetric calculations each segment of the tract is represented as an idealized geometric figure. Estimates of dose to tissues of the GI tract from non-penetrating radiations emitted in the contents of the tract are based on simplistic assumptions expected to overestimate doses to radiosensitive cells in the tract walls. For beta and alpha emitters the dose is taken as 100% and 1%, respectively, of the dose at the surface of the contents.

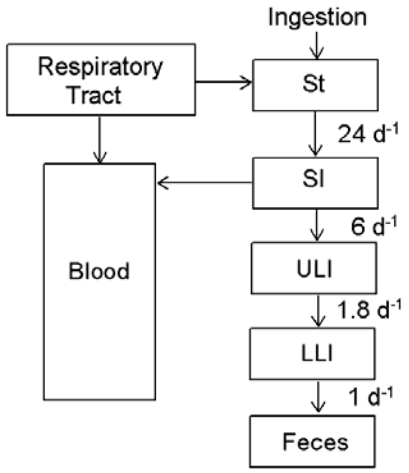

Figure 1. Structure of the GI tract model used by the ICRP since the late 1970s.

Although developed specifically for calculation of doses to workers, the Pub30 model has been used by the ICRP and national agencies to estimate doses to members of the public. Applications to the public have accounted for changes with age in the mass and dimensions of the GI tract and elevated absorption of some radionuclides in infants and children, but the rate of transit of activity through segments of the tract has been assumed to be invariant with age and gender.

Numerous studies of transfer of material through the alimentary tract have been conducted since the late 1970s, and better information is available on absorption and retention in different regions of the tract and on the location of sensitive cells. In the late 1990s an ICRP task group was appointed to develop a biokinetic and dosimetric model of the alimentary tract that reflects the improved information and addresses current needs in radiation protection. The new age- and gender-specific model, called the Human Alimentary Tract Model (HATM), has been completed and will replace the Pub30 model in upcoming ICRP documents.

The purposes of this paper are to discuss the basis for the structure and parameter values of the HATM, summarize the uncertainties associated with selected features and types of predictions of the HATM, and examine the sensitivity of dose estimates to those uncertainties for selected radionuclides. The emphasis of the paper is on biokinetic features of the HATM, particularly transit times through the lumen of the tract, but key dosimetric features of the model are outlined, and the sensitivity of tissue dose estimates to uncertainties in these features are examined for selected radionuclides. No attempt is made here to provide a complete description of the database used in the development of the HATM; rather, illustrative data are provided in graphical form. The reader is referred to Chapter 6 and Appendix C of the HATM report, to be published in 2006, for a more detailed discussion of the database and a full list of publications underlying the transit model.

This paper is the fourth in a series of publications addressing the reliability of the ICRP's dose coefficients for members of the public (Leggett, 2001; Harrison et al., 2001; Leggett, 2003). Previous papers have examined the qualitative sources of uncertainty in the ICRP's biokinetic models (Leggett, 2001); uncertainties in the gastrointestinal absorption fractions (Harrison et al., 2001), and the systemic biokinetics of plutonium from a historical perspective (Leggett, 2003).

2. OVERVIEW OF THE HATM

The structure of the HATM is shown in Figure 2. The compartments and paths of movement represent the following processes: entry of a radionuclide into the oral cavity by ingestion or into the oesophagus after mechanical clearance from the respiratory tract; sequential transfer through the lumen of the oral cavity, oesophagus, stomach, small intestine, and segments of the colon, followed by emptying in faeces; radionuclide deposition and retention on or between the teeth and return to the oral cavity; deposition and retention in the oral mucosa or walls of the stomach or intestines; transfer from the oral mucosa or walls of the stomach or intestines back into the lumenal contents or into blood (absorption); and transfer from secretory organs or blood into the contents of segments of the tract.

Entry into the alimentary tract by ingestion or transfer from the respiratory tract and sequential transfer through the lumen of the tract are regarded as generic processes, in that the rates are assumed to be independent of the radionuclide or its form. The other

processes addressed by the HATM occur at rates that are assumed to depend on the element (and in some cases on the form of the element) taken into the body. For example, element-specific parameter values are required to define the extent of uptake and retention on the teeth or in the walls of the tract or transfer through the walls to blood. An element-specific process is addressed in HATM applications only if information is available to assign a non-zero transfer rate to that process. For most elements, specific information on the behavior of an element in the alimentary tract is limited to total absorption to blood. Radionuclide-specific transfer coefficients for the HATM will be assigned in ICRP documents in which the HATM is applied.

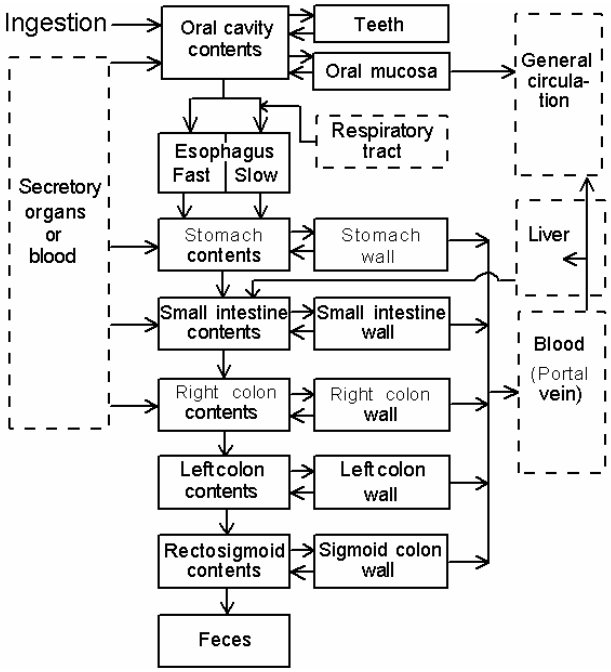

Figure 2. Structure of the HATM. The dashed boxes are not part of the HATM but are included in the schematic to show connections with the respiratory and systemic models.

First-order kinetics is assumed in the HATM. The residence times of material in the lumen of segments of the alimentary tract were initially estimated in terms of the mean transit time because this is the form in which data on GI tract motility generally are reported. The transit time of an atom in a region of the tract is the length of time that it resides in that region, and the transit time of a substance in a region (also called the mean transit time) is the mean of the distribution of transit times of its atoms. The first-order transfer rate or "emptying rate" used to represent a transit time T hours in a segment of the alimentary tract is 1/T per hour, and the corresponding biological half-time in the segment is (ln2)·T hours. Transit times of lumenal contents are regarded as primary parameter values of the HATM, and the first-order transfer rates derived from those transit times are regarded as secondary values.

Separate transit times were developed for transfer of ingested solids, liquids, and total diet through the mouth and oesophagus and for transit of non-caloric liquids, caloric liquids, solids, and total diet through the stomach. The material-specific values were developed for application to special cases. It is anticipated that transit values for total diet will be used as default values.

For purposes of calculating absorbed fractions for short range radiations originating in the contents of the alimentary tract, the segments of the tract are represented as a set of idealized geometric figures and the contents as a homogenous material. For example, the stomach is treated a as sphere, and all tubular regions of the alimentary tract (oesophagus, small and colon) are treated as right circular cylinders.

Organ masses and dimensions are specified for newborn infants, 1-, 5-, 10- and 15-year-old children and adult males and females and are consistent with information given in ICRP Publication 89 on Basic Anatomical and Physiological Data for use in Radiological Protection (ICRP, 2002). The reference anatomical data are used to compute values of Specific Effective Energy (SEE values) for the above age groups. SEE values for intermediate ages are derived by interpolation, generally linear interpolation by inverse body mass.

With regard to estimation of dose from radionuclides entering the lumen of the tract, the HATM differs from the Pub30 model in two main ways. First, retention of radionuclides in the walls of the tract can be specified in the HATM when information is available. This feature can result in substantial increases in the estimated dose to the walls. Second, the location of sensitive cells of different regions of the tract is modeled explicitly in the HATM. The targets for all effects are taken to be the epithelial stem cells which are known to be removed by some distance from the lumen of the tract. Assigned depths of target cells in adult males are given in Table 1. For a number of alpha and beta emitters, this change from the Pub30 model results in substantially reduced dose estimates because alpha emissions and low-energy beta emissions originating in the contents of the tract do not penetrate to the depth at which the sensitive cells are thought to reside.

Table 1. Summary of target cells depths and masses for each target region of the HATM for adult males.

Region	Target cell depth (μm)	Target cell mass (g)
Oral cavity	190-200	0.23
Oesophagus	190-200	0.091
Stomach	60-100	0.62
Small intestine	130-150	3.6
Right colon	280-300	1.3
Left colon	280-300	1.2
Recto-sigmoid	280-300	0.73

3. BASIS OF THE TRANSIT MODEL

This section summarizes the basis for the model of transit of material through the lumen of the alimentary tract. The following topics are addressed for each of the modeled segments of the tract: the main processes to be modeled as described in modern textbooks (e.g., Johnson, 1998); typical values and variability of reported transit times; and compartments and reference transit times used to represent the processes and transit information. Variability in reported transit data is emphasized as an important source of uncertainty in the determination of typical transit times in the population and in applications of the HATM to individual cases.

3.1. Oral cavity

A radionuclide enters the oral cavity in ingested material or by secretion of absorbed activity in saliva. The residence time of ingested material in the mouth is highly variable (Figure 3), depending on the composition and texture of food, the level of hunger, age, personal habits, customs, and other factors. Liquids typically are removed from the mouth in a single swallow in which a posterior movement of the tongue forces the liquid into the oropharynx. Solids typically are chewed for a sufficient time to reduce particles to a few cubic millimeters. The particles may be largely removed from the mouth in a single swallow or two closely spaced swallows, but complete removal sometimes requires several swallows between periods of chewing.

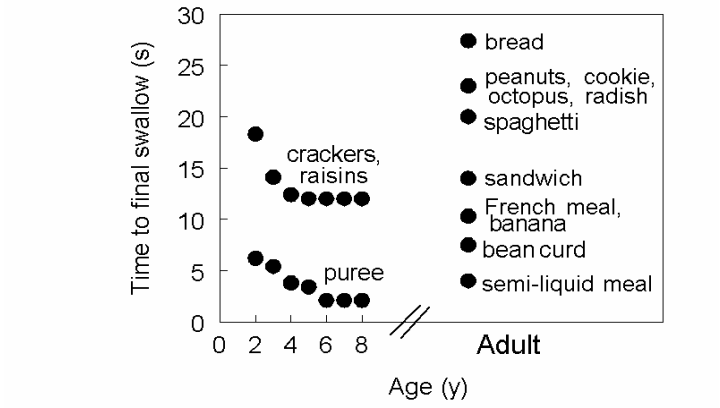

Figure 3. Illustration of data used to derive reference transit times for ingested material in the oral cavity (based on data of Gisel, 1988; Gisel and Patrick, 1988; Horio and Kawamura, 1989; Guy-Grand et al., 1994; Hiiemae and Palmer, 1999; Hoebler et al., 2000).

In the HATM the oral cavity is divided into three compartments: contents (ingested material and saliva), teeth, and oral mucosa. Depending on the element, a small portion of the amount entering the oral cavity may bind to the surface of the teeth or may be absorbed to blood through the oral mucosa. Transfer from the oral cavity contents to the

oesophagus by swallowing is described by generic transit rates, with separate rates provided for activity in liquids, solids, and total diet. Element-specific transfer rates must be selected to describe transfer between oral cavity contents and teeth or oral mucosa, or transfer from oral mucosa to blood. Any transfer of activity into the oral cavity contents in saliva must be specified in the systemic biokinetic model for an element.

Baseline transit times for the oral cavity (Table 2) were based on reported measurements of time to first swallow or final swallow of different materials at different ages as illustrated in Figure 3. For conversion of reported data to transit times, the assumptions were made that the transit time of a liquid is the time from intake to first swallow and the transit time of a solid is three-quarters of the time from intake to final swallow. The residence time of secreted saliva was assumed to be the same as that of food. Transit times in the oral cavity were assumed to be independent of age after infancy because differences with age in measured swallowing times for specific foods may be largely offset by changes in diet.

Table 2. HATM baseline transit times for the oral cavity.

Ingested material	Transit time (s)	
	Infant	Ages $\geq$ 1 y
Solids	--	15
Liquids	2	2
Total diet	2	12

The baseline values in Table 2 could substantially under- or over-estimate actual transit times in specific cases. The residence time in the mouth can be increased by up to an order of magnitude by some diseases that interfere with chewing or swallowing such as poliomyelitis and encephalitis.

3.2. Oesophagus

When material is swallowed, a coordinated and sequential set of peristaltic contractions produces a zone of pressure that moves down the oesophagus with the bolus in front of it. As the bolus approaches the lower oesophageal sphincter, the sphincter relaxes, allowing the bolus to enter the stomach. The time required for the wave to travel from the pharynx to the stomach typically is 5-12 sec.

The oesophagus may not be totally emptied by the original peristaltic contraction initiated by the swallow. The distension induced by residual material initiates another peristaltic contraction, called a secondary peristalsis, in the absence of a swallow. Several secondary contractions often are required to remove the remaining material, and some material can remain for several minutes or even hours in the oesophagus.

In the HATM oesophageal transit is represented by two components: a fast component representing movement in front of the initial peristaltic contraction initiated by the swallow, and a slow component representing transfer of residual swallowed material. For lack of specific information, the slow component is applied to mucus and associated

material entering the oesophagus via the oropharynx after escalation from the respiratory tract.

The average time required for material to transfer to the lower oesophageal sphincter may be slightly less than the time required for the original peristaltic wave to travel that distance, depending on the physical nature of the swallowed material and the contribution of gravity. For example, liquids swallowed in an upright position may reach the stomach before the peristaltic wave. Figure 4 illustrates reported differences with material, body position, and age in the fast component of oesophageal transit.

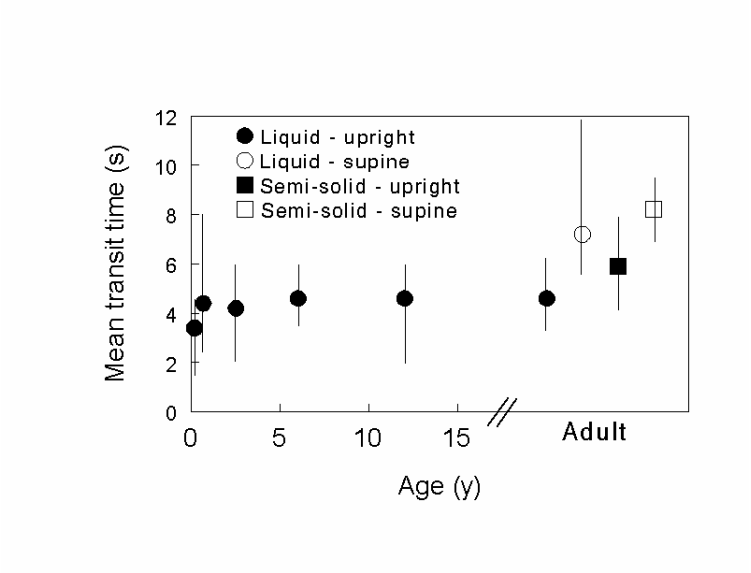

Figure 4. Differences with age, food type, and body position in transit times through the lumen of the oesophagus (fast component). Symbols represent means and vertical lines represent ranges of individual observations for children and reported central values for adults (Guillet et al., 1983; Kjellen and Svedberg, 1983; Ham et al., 1984; De Vincentis et al., 1984; Klein and Wald, 1984, 1987; Sand et al., 1986; Glinoer et al., 1987; Jorgensen et al., 1992; Stacher and Bergmann, 1992; Chang et al., 1995; Baulieu et al., 1996; Nguyen et al., 1997; Aly, 2000).

Baseline transit times for material in the oesophagus are given in Table 3. Separate transit times for solids, liquids, and total diet were derived for completeness, to reflect that differences in transit times of liquids and solids through the oesophagus are discernable from clinical and experimental data.

Table 3. HATM baseline transit times for the oesophagus.				
Ingested material	Transit time for infants (s)		Transit time for ages ≥ 1 y (s)	
	Fast (90%)	Residual (10%)	Fast (90%)	Residual (10%)
Solids	--	--	8	45
Liquids	4	30	5	30
Total diet	4	30	7	40

Oesophageal transit can be strongly affected by a number of conditions including hiatal hernia, oesophageal reflux, oesophageal spasm, oesophageal diverticulosis, and achalasia. Transit is particularly slow in persons with achalasia, a condition in which the lower oesophageal sphincter fails to relax during the swallowing mechanism. In achalasia, the residual component often represents half or more of the swallowed material. When achalasia becomes severe, the oesophagus may not empty swallowed food for many hours.

3.3. Stomach

The kinetics of gastric emptying is affected by many factors, including composition of the ingested material, gender, and age. Emptying times generally increase in the order non-caloric liquids < caloric liquids < solids.

Emptying of liquids usually begins within 1-3 min of their arrival in the stomach and can be described reasonably well by a mono-exponential function, although a lag-phase of several minutes has been reported for liquids of high caloric density. Removal of the solid component typically consists of an initial lag-phase of several minutes in which there is relatively slow emptying, followed by an extended phase of nearly linear emptying. Non-digestible solids are retained in the stomach until the digestible solids have been evacuated. During the latter stages of gastric emptying, a series of migrating motor complexes occurring at regular intervals move distally through the stomach, effectively sweeping the non-digestible solids into the small intestine (Stubbs 1991, 1992; NCRP, 1998).

For healthy adult subjects, reported central values for observed gastric half-emptying times range from 40 to 160 min for solids, 8 to 107 min for caloric and unspecified liquids, and 15 to 35 min for liquids clearly identified as non-caloric (e.g., Horowitz et al., 1985; Brophy et al., 1986; Gilbey and Watkins, 1987; Gill et al., 1987; Rao et al., 1987; Datz et al., 1987; Hutson et al., 1989; Dalvi et al., 1990; Lin et al., 1994; Hermansson and Sivertsson, 1996; Gryback et al., 1996; Schvarcz et al., 1997; Bennink et al., 1998; Ploutz-Snyder et al., 1999; Chen et al., 2000; Tougas et al., 2000). The means of collected central values are approximately 90 min for solids with coefficient of variation (CV) ~30%, 35 min (CV ~ 60%) for caloric and unspecified liquids, and 25 min (CV ~ 30%) for non-caloric liquids. The rate of gastric emptying of ingested material

depends strongly on its composition and the level of nutrients in the jejunum. The emptying time increases nearly linearly with the caloric content of the meal and also is increased substantially by fat. Gastric emptying times are altered by a number of diseases, including several diseases that affect the nervous system or alter energy requirements.

Reported emptying times of either solids or caloric liquids are greater on average in women than in men (Figure 5). Based on various measures of central tendency including the median, mean, weighted mean, and trimmed weighted mean, a typical or central half-emptying time for solids is about 75-80 min in adult males and 100-110 min in adult females; for caloric liquids, a typical half-emptying time is 30-35 min in males and 40-45 min in females; for non-caloric liquids, a typical half-emptying time for either gender is about 20-25 min (e.g., see Scarpignato et al., 1983; Notivol et al., 1984; Brophy et al., 1986; Gill et al., 1987; Rao et al., 1987; Datz et al., 1987; Hutson et al., 1989; Lin et al., 1994; Hermansson and Sivertsson, 1996; Gryback et al., 1996; Schvarcz et al., 1997; Bennink et al., 1998; Tougas et al., 2000**)**. Differences with gender appear to diminish with aging due to an increase in the emptying rate in females, perhaps beginning after menopause.

Reported gastric half-emptying times for meals in infants vary with the type of milk ingested, the maturity of the infant, and the measurement technique (Signer et al., 1975; Cavell, 1982; Ewer et al., 1994, 1996; Veereman-Wauters et al., 1996; Barnett et al., 1999; Van Den Driessche et al., 1999). Reported values range from 15 to 100 min and average about 50-55 min. The half-emptying time of water in healthy infants appears to be only a few minutes. Reported gastric emptying times for toddlers, young children, and adolescents generally are within the range of values determined for adults (Magazzu et al., 1987; Smith et al., 1990, 1993; Collins et al., 1997; Montgomery et al., 1998; Chiloiro et al., 1999; Gatti et al., 2000).

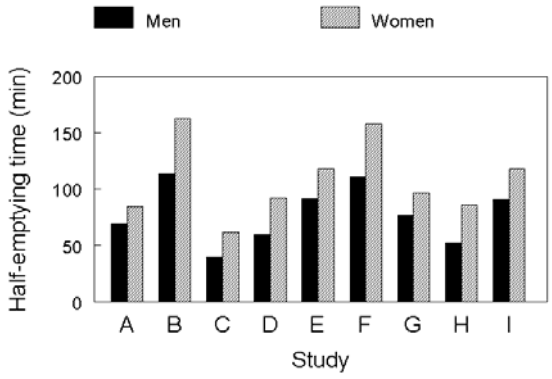

Figure 5. Comparison of gastric half-emptying times of solids in adult male and female subjects in nine studies (data of Scarpignato et al., 1983; Notivol et al., 1984; Rao et al., 1987; Datz et al., 1987; Hutson et al., 1989; Hermansson and Sivertsson, 1996; Gryback et al., 1996; Bennink et al., 1998; Tougas et al., 2000).

In the HATM the stomach is divided into compartments representing the contents and the stomach wall. These compartments are used to represent transfer of the contents to the small intestine, temporary retention of activity in the stomach walls, absorption from the contents or walls to blood, and secretion into the stomach contents. The last three processes are assigned non-zero transfer rates only when element-specific information is available.

Separate baseline transit times for the stomach are provided for solids, caloric liquids, and non-caloric liquids (Table 4). Age- and gender-specific values are provided for each case.

Table 4. HATM baseline transit times for the stomach.

Ingested material	Transit time (min)			
	Infant	Age 1-15 y	Adults	
			Males	Females
Solids	--	75	75	105
Liquids				
Caloric	75	45	45	60
Non-caloric	10	30	30	30

3.4. Small intestine

The motility patterns of the small intestine are organized to optimize its primary functions of digestion and absorption of nutrients and absorption of fluids and electrolytes. Movement of most of the material through the small intestine after a meal is a nearly linear process, but migrating motility complexes in the fasting human that clear undigested residue are spread unevenly over time. Almost all nutrient absorption occurs in the proximal portions of the small intestine, the duodenum and jejunum. The ileum, the distal part of the small intestine, acts as a reservoir and intermittently transfers boluses of variable sizes into the colon. Intake of a subsequent meal may stimulate transfer into the colon, but this appears to depend on the composition of the material in the ileum.

In the HATM the small intestine is divided into compartments representing the contents and the wall. These compartments are used to represent the following processes: transfer of the contents to the right colon, temporary retention of activity in the wall of the small intestine, absorption from the contents or walls to blood, and secretion into the small intestine contents. Some substances may be retained in the wall of the small intestine temporarily before absorption to blood or return to the intestinal contents.

Reported transit times based on techniques other than the hydrogen breath test are in the range 1.8-8 h, with most values near 3-4 h (Cann et al., 1983; Davis et al., 1986; Read et al., 1986; Kerlin et al., 1989; Ewe et al., 1989; Fallingborg et al., 1989, 1990; Birkebaek et al., 1990; Lartigue et al., 1991; Caner et al., 1991; Madsen and Hendel, 1992; Argenyi et al., 1995; Adkin et al., 1995; Degen et al., 1997; Kagaya et al., 1997; Sharpstone et al., 1999; Brinch et al., 1999). The mean of collected values is about 4 h (CV ~ 40%).

Limited comparisons of small intestinal transit in adult males and females have not revealed significant differences with gender. Most investigations of age dependence in the transit time through the small intestine have been based on the hydrogen breath test, which gives questionable results. Limited data based on other techniques suggest that transit through the small intestine and orocecal transit are similar in children, young adults, and elderly persons.

Baseline transit time through the small intestine: 4 h
(independent of age, gender, and material)

Reported transit times through the small intestine vary by more than a factor of 4, but differences in reported values may result largely from measurement difficulties for this region of the tract. The transit time through the small intestine may be decreased by diarrhea and increased by constipation but, in contrast to colonic transit, does not appear to be highly sensitive to these conditions. The transit rate may be altered by stress, physical exercise, pregnancy, some pharmaceuticals, and some diseases, but reported data on the effects of the factors are not definitive.

3.5. Colon

The colon absorbs water and electrolytes that enter from the small intestine or in secretions and stores faecal matter until it can be expelled. Absorption of other materials from the colon is also known to occur; for example, substances administered as suppositories can be absorbed from the colon after retrograde movement of contents from the rectum into the sigmoid colon.

Flow of material in the colon is slow and highly variable. Periods of contraction between longer periods of quiescence result in mass movements of colonic material a few times during the day. Most of the movements of the proximal colon are weak peristaltic contractions that serve to mix contents back and forth, exposing them to absorptive surfaces. Typically 1-3 times a day, peristaltic contractions move significant amounts of material from one region of the colon to another. One mass movement may transport contents from the transverse to the sigmoid colon or rectum. The rectum serves mainly as a conduit but can also serve as a storage organ when the mass received from the sigmoid colon is too small to evoke the recto-anal inhibitory reflex that signals the need to defaecate, or when this reflex is neglected.

The HATM divides the colon into the right colon, left colon, and rectosigmoid, a division often used for diagnostic and experimental examinations of colonic transit. This division was chosen to make best use of experimental data and is expected to allow best available estimates of the time-dependent distribution of activity in the colon. Each of the major segments of the colon is further divided into a compartment representing contents and a second compartment representing the wall. These compartments are used to represent sequential transfer of contents through the segments, retention of activity in the walls,

absorption from the colon to blood, and secretion into the colon. All secretions into the colon are assigned to the right colon contents for simplicity and dosimetric conservatism.

Central estimates of the colonic transit time by different investigators vary by about a factor of 4 (17-68 h), but most reported values are in the range 24-48 h (Arhan et al., 1981; Chaussade et al., 1986; Metcalf et al., 1987; Rao et al., 1987; Fallingborg et al., 1989, 1990; Birkebaek et al., 1990; Talley et al., 1990; Klauser et al., 1990, 1992; Bautista Casasnovas et al., 1991; Basile et al., 1992; Bergmann et al., 1992; Madsen and Hendel, 1992; Meier et al., 1995; Folwaczny et al., 1995; Pigeon et al., 1997; Zaslavsky et al., 1998; Bougle et al., 1999; Bouchoucha and Thomas, 2000; Santos et al., 2000). Collective data (Figure 6) as well as data from individual studies involving both genders indicate that transit through the colon is substantially slower on average in women than in men. Mean transit times appear from collective data to be shorter on average in children than adults (Figure 6), but the studies of children have often been under much different conditions than those on adults. Age-specific data on the time to first appearance of ingested carmine red or other markers in faeces that are used to diagnose bowel function suggest an increase with age in transit times from infancy to adulthood.

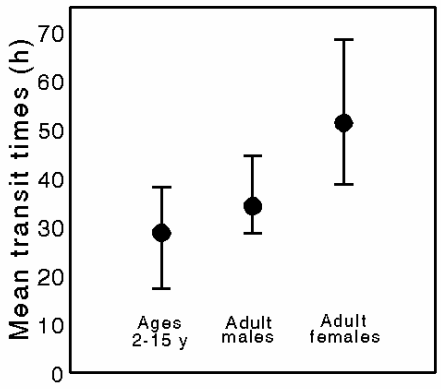

Figure 6. Ranges (vertical bars) and overall means (circles) of collected central colonic transit times for groups of normal children, adult males, or adult females.

Baseline transit times through segments of the colon are age- and gender-specific (Table 5). Baseline values are independent of the material entering the colon.

Table 5. Baseline transit times for segments of the colon (all material).

Segment	Transit time (h)				
	Infant	1 y	5-15 y	Adult male	Adult female
Right colon	8	10	11	12	16
Left colon	8	10	11	12	16
Rectosigmoid	12	12	12	12	16

Average oro-rectal transit times, expected to represent primarily colonic transit, vary substantially from one region of the world to another, presumably due mainly to differences in diet, particularly the level of intake of fiber. Central estimates of the colonic transit time by different investigators vary by about a factor of 4 (17-68 h). Colonic transit times may be a small percentage of the baseline values in persons with diarrhea and may be several days in constipated persons. A number of disease states affect colonic transit. The transit time through the colon may be altered substantially by drugs.

4. UNCERTAINTIES IN MODEL FEATURES AND PREDICTIONS

4.1. Definitions

The authors' judgments concerning uncertainties in features or predictions of the HATM are summarized below, either qualitatively or in terms of a quantitative uncertainty factor (UF). An uncertainty factor was determined by first assigning a subjective confidence interval [A,B] such that the true but unknown value was judged with reasonably high confidence (90% was used as a reference value) to lie between A and B. The associated uncertainty factor UF is defined as $(B/A)^{1/2}$. The quantity may be considered to be known within a factor of $(B/A)^{1/2}$ in the sense that all values in the subjective confidence interval [A,B] are within a factor of $(B/A)^{1/2}$ of the geometric mean of A and B (see Leggett, 2001).

4.2. Uncertainties in model formulation

4.2.1. Divisions of the alimentary tract into compartments

With the exception of the division of the colon, the compartments used in the HATM to describe transfer of material through the lumen of the alimentary tract represent anatomically and functionally distinct regions of the tract. The colon has been divided in a number of different ways in radiation protection models. The model of Publication 30 divided the colon into the upper large intestine (ULI) and the lower large intestine (LLI), where the ULI includes the ascending and transverse colons and the LLI includes the descending colon, sigmoid colon, and rectum. A model developed for use in nuclear medicine (Stubbs, 1991, 1992; NCRP, 1998) divided the colon into the ascending colon, transverse colon, and rectosigmoid. The HATM divides the colon into the right colon, left colon, and rectosigmoid. The right colon is defined as the caecum, ascending colon, and proximal half of the transverse colon; the left colon is the distal half of the transverse colon plus the descending colon; and the rectosigmoid is the sigmoid colon plus the rectum. This division is often used for diagnostic and experimental examinations of colonic transit, and considerable information is available on transit times through each of these three segments. It was concluded that the division of the large intestine into right colon, left colon, and rectosigmoid allows best estimates of the time-dependent distribution of ingested, inhaled, or secreted activity in the colon, based on modern data.

The HATM Task Group considered whether the rectum should be represented as a separate compartment, since it is commonly assumed to function mainly as a conduit rather than a storage organ. Information found in the literature indicated, however, that the rectum can serve for extended periods as a storage organ and in some cases could contain a substantial portion of the total activity in the alimentary tract. For example, Notghi et al. (1993) used a polymer-coated capsule to deliver ^{111}In-resin into the ileocaecal region in eight volunteer subjects and at 24 hours found activity mainly in the rectum in two of the subjects. In a study involving 48 healthy volunteers (mean age 38.4 +/-15.8 SD years; 30 men, 18 women), Shafik et al. (1997) investigated whether the rectum serves as a storage organ as well as a conduit. Stools in the rectum were found in about two-thirds of the subjects. The subjects with an empty rectum had their last defaecation 5.2 +/- 3.6 h before examination, and the subjects with a partially filled rectum had their last defaecation 15.6 +/-12.9 h earlier. In view of such findings, and because of the difficulties in determining a meaningful transit time separately for the rectum, it was concluded that the rectum should not be treated as a separate compartment.

4.2.2. Use of first-order kinetics

The assumption of first-order kinetics is made for computational convenience. The removal half-times of luminal contents from segments of the tract are set to produce the average residence times of stable atoms implied by the reference transit times summarized earlier. The intent is to produce reasonable central estimates of the cumulative activity of radionuclides in the contents of the segments using relatively simple kinetics.

For relatively short-lived radionuclides, first-order kinetics could overestimate decays in the lower regions of the tract because it implies an immediate appearance of some ingested atoms in all regions of the tract. For example, an ingested radionuclide with half-life 20 min is likely to decay almost entirely between the mouth and caecum (ignoring absorption to blood) because more than 10 radiological half-lives may elapse before the first appearance of the ingested material in the right colon. The HATM predicts on the basis of first-order kinetics that about 3% of the total decays in the alimentary tract would occur in the colon after ingestion of a radionuclide with half-life 20 min.

As a first-order model, the HATM predicts continuous faecal excretion of activity starting immediately after ingestion, resulting in an overestimate of early faecal excretion. For example, for an adult male the model predicts that faecal excretion during the first half day after intake is about 3% of the ingested amount, in the absence of radiological decay or absorption to blood. By contrast, studies indicate that the first appearance of ingested markers in faeces of healthy adults is usually more than 12 h.

HATM predictions of cumulative faecal excretion over periods of 1 d or longer appear to be reasonable central estimates for the population. When using the HATM or any other gastrointestinal model for interpretation of bioassay data, however, it should be kept in mind that the pattern of faecal excretion of ingested material is highly variable and difficult to predict in individual cases. This is illustrated in Figures 7 and 8, which

compares HATM predictions with observed patterns of faecal excretion after ingestion of ^{85}Sr and ^{26}Al, respectively. The ^{85}Sr study (Likhtarev et al., 1975) involved nine young adult males, and the ^{26}Al study (Priest et al., 1998) involved two young adult males. For purposes of this comparison, total faecal excretion was defined as faecal excretion of unabsorbed activity over the first five days after ingestion. No attempt was made to adjust observations for endogenous secretion of absorbed activity into the intestines during that time; this is expected to represent roughly 2% of ingested ^{85}Sr on average but almost none of ingested ^{26}Al. In the case of ^{85}Sr, the HATM yields reasonably accurate predictions of the median daily faecal excretion rates over the first five days but poor estimates for some individuals (Figure 7). Both subjects of the ^{26}Al study excreted more than 90% of ingested activity during the first two days, compared with HATM predictions of only 69% over two days (Figure 8). While the HATM did not closely predict day-by-day faecal excretion of activity by these two subjects, HATM predictions of cumulative activity of ingested ^{26}Al in the alimentary tract of adult males, 169 Bq-d, agrees reasonably well with the values of 149 and 179 Bq-d calculated from measured excretion of activity in the two subjects.

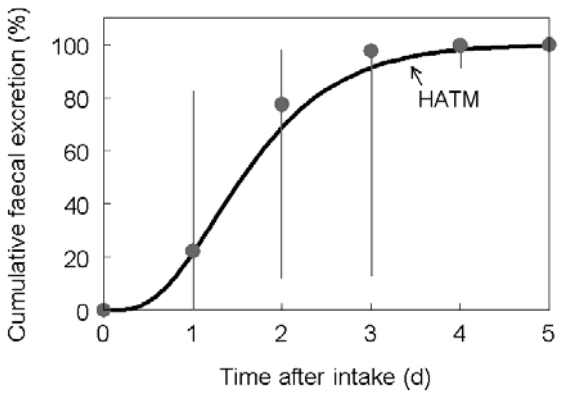

Figure 7. HATM predictions of cumulative faecal excretion (relative to five-day faecal excretion) compared with observations for ingested ^{85}Sr (Likhtarev et al., 1975). Circles and vertical lines represent medians and ranges, respectively, of values determined for nine young adult males.

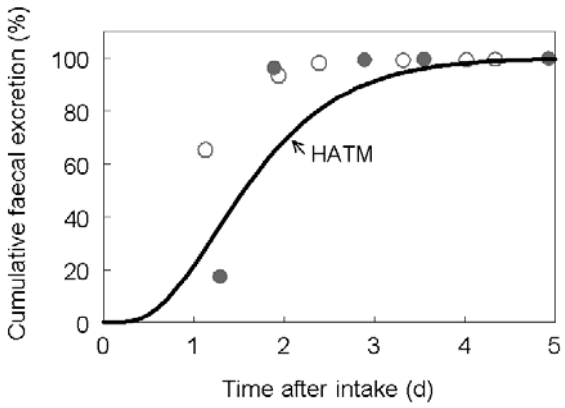

Figure 8. HATM predictions of cumulative faecal excretion (relative to five-day faecal excretion) compared with observations for two adult male subjects who ingested ^{26}Al in drinking water (Priest et al., 1998).

4.2. Uncertainties in transit times

In the years since the development of the Publication 30 model (ICRP, 1979), numerous investigations of the kinetics of material in the alimentary tract have been conducted by improved, non-invasive techniques, such as external viewing of radio-labeled foods, liquids, or indigestible substances. While uncertainties associated with measurement techniques have been substantially reduced, the difficulties involved in determining true transit times should not be underestimated. For example, the physical characteristics of markers used in modern studies apparently can affect colonic transit times (Olmos et al., 1994). Also, some methods still in common use do not appear to provide representative or reproducible results.

Uncertainties also are inherent in the assumptions and algorithms used to translate measurements into estimates of the mean transit time. For example, measurements of colonic transit frequently are based on counts of ingested radio-opaque markers in the regions of interest. It has been argued that this technique may substantially underestimate actual transit times in many cases because the experimental methods may not closely approximate the underlying assumptions of continuous ingestion of markers and attainment of steady-state by the time of counting (Bouchoucha and Thomas, 2000). The extent of underestimate may vary considerably from one study to another due to differences in numbers and patterns of administration of the marker and times of measurement.

Considering the limitations of measurement techniques and the variability in reported average residence times in different segments of the alimentary tract, the transit time of material in the oral cavity or oesophagus is judged by the authors to be known with a factor of 2 (UF = 2); and the transit times of material in the stomach, small intestine, right

colon, left colon, or rectosigmoid colon in the adult male are judged to be known within a factor of about 1.5 (UF=1.5). As discussed earlier, each of these uncertainty factors refer to the level of knowledge of the central value in the world population (for the age, gender, and ingested material of interest) and not the expected accuracy for individual cases.

Based on the UF for colon, the sensitivity of effective dose coefficients and equivalent dose coefficients to the colon to the uncertainty in the colonic transit time was examined for ingestion of ^{90}Sr, ^{106}Ru and ^{239}Pu by an adult male. In the cases of ^{90}Sr and ^{106}Ru the implied UFs for colon dose were 1.5 and 1.4 respectively, which are nearly the same as that for transit time, reflecting their close association. For ^{239}Pu, colon dose is projected to arise solely from activity absorbed to blood, so that variations in transit time should have no effect on the dose estimate.

For ^{106}Ru the colon dose from activity in the contents makes an important contribution to effective dose, and the potential errors in transit times yield a UF for effective dose of about 1.2. For ^{90}Sr, however, colon dose contributes little to the effective dose, which is virtually unaffected by potential errors in estimated gastrointestinal transit times.

Table 6. Uncertainty Factors (UF) and ratios of dose coefficients (B/A) resulting from uncertainty in transit times in the colon[a], considering ingestion by adult males.

Nuclide	Colon dose		CED[b]	
	B/A[c]	UF[d]	B/A	UF
^{90}Sr	2.3	1.5	1.0	1.0
^{106}Ru	2.0	1.4	1.3	1.2
^{239}Pu	1.0	1.0	1.0	1.0

a- for colon transit time, B/A = 2.3 (18/8), and UF = 1.5 ($\sqrt{2.3}$)
b- committed effective dose.
c- A and B values correspond to 5th and 95th percentile confidence intervals.
d- UF = $(B/A)^{1/2}$.

4.3. Uncertainty in anatomical features

The dimensions and geometrical configurations of the structures of the tract were formerly estimated from measurements on cadavers, and those estimates often did not closely reflect conditions in the living body. More accurate determination of the geometry of the gastrointestinal tract of a living person has become possible with the advent of external visualization techniques with high resolution. Nevertheless, it remains difficult to determine typical sizes, shapes, and relative positions of structures of the tract with high accuracy due to the considerable variability in these features from one person to another and from one body position to another in the same person.

A UF of about 1.4 seems appropriate for the dimensions (e.g., length, width, or internal diameter of a segment of the intestines) of most structures within the alimentary tract. Dose estimates to radiosensitive cells in the tract walls are relatively insensitive to the

uncertainty in the geometry of the tract (as represented by this UF) for relatively high-energy photons but are sensitive to this factor for beta radiation or low-energy photons. As an illustration, consider the sensitivity of dose to radiosensitive cells of the intestines to the uncertainty in the diameter of the intestines, for beta emitters in the intestinal contents. Strontium-90 (mean beta energy = 0.20 MeV) and its short-lived decay product, yttrium-90 (half-life, 64 h; mean beta energy = 0.94 MeV) are chosen as an example involving dose from relatively low and relatively high energy beta particle emissions. Based on an assigned UF of 1.4 for the diameter of the intestines, the resulting UF for dose to the wall from $^{90}Sr/^{90}Y$ is about 1.9. In contrast to most parameters, this is a case where UF for the result (dose) is larger than that in the parameter (diameter). This is because the UF in the cross-sectional area of the section, which is an indicator of the extent of energy absorption within the lumen, is 2 for a UF of 1.4 in the diameter. However, such uncertainties in colon dose from $^{90}Sr/^{90}Y$ will have a negligible effect on committed effective dose in this case, because the latter is dominated by doses to tissues from activity absorbed to blood.

4.4. Uncertainty in location of target regions for cancer induction

Doses are calculated separately for the mucosal layer of each region of the HATM. For penetrating radiations, the average dose to the walls of each region is used as a measure of the dose to the mucosal layer. For non-penetrating alpha and beta particle emissions originating in the contents of the tract, the dose is dependent on assumptions regarding the location of target cells for cancer induction. For each region of the alimentary tract, the target is taken to be the stem cells that are located in the basal layer of the stratified squamous epithelia of the mouth and oesophagus and within the crypts that penetrate the mucosal layer in the stomach and small and large intestines.

Table 7 summarizes results of a limited analysis of the sensitivity of dose to the colon from alpha or beta emitters in the lumen due to the uncertainty in the location of target cells. The results are normalized to the default assumption that the sensitive cells form a continuous layer at a depth of 280 – 300 μm from the lumenal surface of the colon. As illustrated in Columns 2 and 3, the dose to the target region was found to be relatively insensitive to the depth of radiosensitive cells. Similarly, widening the target to 200 – 300 μm to include cells at higher positions than the stem cells, to take account of possible bystander communication of damage (Goldberg and Lehnert, 2002), also has little effect on doses (column 4). The possibility addressed in the last column of Table 7, that target cells could be distributed over depths from 0-300 μm, is an extreme situation based on the possibility that neoplastic changes may be initiated in cells on the lumenal surface. Although it is generally accepted that it is the stem cells in the bases of the crypts that are the targets for cancer induction, some uncertainty has been raised by observations of dysplastic cells on the lumenal surface of the colon between apparently normal crypts (Shih et al. 2001), although this is challenged by other authors (Preston et al. 2003). As shown in Table 7, extending the target to 0 – 300 μm results in larger increase in doses. The increase by factors of about 1.5 for ^{234}U and 3 for ^{239}Pu are relative to the dose to the colon resulting from activity absorbed to blood (see above). However, these increases in colon doses from ^{234}U and ^{239}Pu will make negligible differences to committed effective

doses, which are dominated by contributions from doses to tissues and organs from activity absorbed to blood.

Table 7. Sensitivity of ingestion dose coefficients for the colon (adult males) to uncertainty in the depth of sensitive cells (values normalized to default case[a])

Nuclide	Assumed location of the target region – depth from lumen, μm.			
	220 – 240	340 – 360	200-300	0-300
Sr-90	7%	-6%	5%	21%
Ru-106	3%	-2%	2%	8%
U-234	0%	0%	0%	148%
Pu-239	0%	0%	0%	317%

[a]Default case assumes a target depth of 280 – 300 μm

CONCLUSIONS

This paper describes the ICRP's updated biokinetic and dosimetric model of the human alimentary tract and considers uncertainties in key aspects of the model. The effects of uncertainties in transit times, anatomical dimensions, and location of target cells in terms of uncertainties in doses to sensitive tissues of the alimentary tract depends on the radionuclide and its radioactive emissions. An important feature of the new model is that doses are calculated to epithelial stem cells in each alimentary tract region as the putative targets for cancer induction. The estimated dose from alpha particles and low energy beta particles emitted in the gut lumen is zero in the new model. This estimate is unaffected by assumptions regarding transit times through the lumen of the tract and is relatively insensitive to assumptions regarding the dimensions of the tract. On the other hand, these two factors can have substantial effect on dose estimates for radionuclides that emit photons and higher energy beta particles. The extent to which uncertainties in alimentary tract doses result in uncertainties in effective dose depends on the radionuclide and the proportion of the effective dose contributed by the alimentary tract.

The updated model will be published this year as ICRP Publication 100. The model will be used in forthcoming calculations of dose coefficients for workers to replace ICRP Publication 30 and subsequently in revisions of dose coefficients for members of the public. The replacement for ICRP Publication 30 will be issued after the new ICRP recommendations and will apply new tissue weighting factors as well as revisions to dose calculation methodology, including the use of new anatomical models and improved approaches to bone dosimetry. Aspects of uncertainties in updated models and approaches to dosimetry and sensitivity of dose estimates to those uncertainties will be addressed in forthcoming journal publications.

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