CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Thorium is not readily absorbed from the lungs or gastrointestinal tract; absorption depends on compound solubility and particle size.
- Thorium distributes primarily to lymph nodes and bone surface, and can be retained in the lungs following inhalation exposure.
- Elemental thorium cannot be metabolized.
- Most inhaled thorium is excreted in the feces following ciliary clearance from the lungs to the gastrointestinal tract. Most ingested thorium is unabsorbed and excreted in the feces.

3.1.1 Absorption

Inhalation Exposure. The absorption of thorium from the lungs is dependent upon the chemical nature of the isotope and the size of the aerosol particle (Boecker 1963; Boecker et al. 1963; Moores et al. 1980; Newton et al. 1981; Sunta et al. 1987; Syao-Shan 1970a). Increasing the particle size (>2 μm) increases deposition in the respiratory tract of mice, but decreases deposition in the alveolar region. A linear relationship was found between aerosol dosage of ^{232}Th and the amount deposited in the alveolar region (Moores et al. 1980). Approximately twice as much ^{234}Th is absorbed from the lungs of rats exposed to soluble thorium citrate (33%) compared to soluble thorium chloride (19%) (Boecker et al. 1963). However, following the initial difference in absorption, thorium shows the same distribution and excretion pattern, regardless of absorbed compound. Syao-Shan (1970a) determined that 1.5–5.0% of the administered amount to rats is absorbed from the lungs 1 day after intratracheal administration of insoluble $^{232}ThO_2$. Deposited ThO_2 tends to remain in the lungs for long periods of time; 68–73% of $^{232}ThO_2$ remained in the lungs after 1 day, while 15–30% remained after 21 months. Thorium is removed primarily by ciliary clearance and is excreted in the feces (Wrenn et al. 1981). ICRP (ICRP 1979) assumes that a total of 5% absorption of inhaled thorium is transferred to the blood. However, the solubilities of the thorium compounds appear to be an important biological factor, as evidenced by differences in toxicity: LD_{50} values after 30 days following intraperitoneal injection in mice were 370.8 mg thorium/kg for soluble ^{232}Th (as thorium nitrate) and 589.1 mg thorium/kg for soluble ^{232}Th (as thorium chloride), while the highest dose (2,000 mg thorium/kg) for insoluble $^{232}ThO_2$ resulted in 10% mortality (1/10), the same rate of death observed among control mice (Syao-Shan 1970b).

Lung levels of ^{230}Th and ^{232}Th in workers occupationally exposed to thorium (miners and millers) are significantly higher than those not occupationally exposed (Gilbert et al. 1985; Singh et al. 1981; Vocaturo et al. 1983; Wrenn et al. 1985). In a review of the epidemiological evidence, Wrenn et al. (1981) concluded that the major route of exposure was inhalation. Although intake of thorium through the air may account for <1% of the total intake, absorption through the lungs accounts for approximately 2/3 of the ultimate uptake in the body. This is due primarily to the low gastrointestinal absorption rate (0.02%) in humans (Maletskos et al. 1969; Sullivan et al. 1983).

Oral Exposure. ICRP has recommended a human gastrointestinal absorption value of 0.02% for all forms of thorium (ICRP 1979). In a review of the literature by Johnson and Lamothe (1989), a human gastrointestinal absorption value of 0.1–1% was calculated. Absorption of thorium (as thorium nitrate) is 40-fold higher in neonatal rats (1.1–1.2%) (Sullivan 1980b; Sullivan et al. 1983) than in adult rats (0.028–0.5%) (Sullivan 1980a; Traikovich 1970).

Absorption of thorium in adult mice was 0.065% (Sullivan et al. 1983). These data suggest that infants may be a susceptible population for exposure. In other studies of actinide elements (including thorium), little variation in gastrointestinal absorption was found between rats, guinea pigs, and dogs. Chemical form, solubility, and particle size were found to be the determinants of absorption (Sullivan 1980a). The absorption of various forms and isotopes of thorium in rats was compared by Pavlovskaia (1973). It was found that the rate of absorption of thorium-ethylenediaminetetraacetic acid (EDTA) by the gastrointestinal tract was 60 times greater than that of thorium dioxide. Thorium nitrate had an absorption rate 4 times greater than thorium dioxide, and the absorption rate of thorium chloride was 10 or 20 times greater than thorium dioxide, depending on concentration. The absorption differences are attributable to different solubilities of the various chemical forms.

Dermal Exposure. No studies were located regarding the rate and extent of absorption of thorium following dermal exposure of humans or animals. Absorption of thorium through the skin of animals can be inferred, however, because testicular effects were seen in rats following application of thorium nitrate directly to the lateroabdominal and scrotal skin (Tandon et al. 1975).

3.1.2 Distribution

Glover et al. (2001) reported on the distribution of ^{232}Th activity in the tissues of a whole-body donor (with no known occupational exposure to thorium) to the U.S. Transuranium and Uranium Registries. The whole-body activity (310 mBq [8.38 pCi] or 76 μg based on a specific activity of 4,080 Bq/g [110.27 nCi/g]) was distributed among the respiratory system (39.1%), skeleton (34.2%), muscle (16.6%), skin (8.39%), tracheobronchial lymph nodes (4.13%), central nervous system (0.329%), liver (0.22%), kidneys (0.11%), spleen (0.065%), and other soft tissues combined (1.1%). The percentages total 104%, perhaps indicating that the thorium content of tracheobronchial lymph nodes was included with the respiratory system entry.

Iyengar et al. (2004) estimated contents of several elements, including thorium, in selected organs of the adult Asian population using measured data from road accident victims in China, India, the Philippines, and Republic of Korea who had been healthy prior to accidental death. Reported thorium contents were 3.96–22.1 μg (median 14.45 μg) in the skeleton, 0.89–7.79 μg (median 3.21 μg) in the lung, and 0.12–0.53 μg (median 0.23 μg) in the liver. The thorium content in the skeleton and liver was considered to have resulted from the ingestion of thorium, whereas inhalation of ambient thorium dust was thought to have been the major route of exposure for the thorium content in the lungs.

Harley and Fisenne (1990) assessed the distribution of uranium and thorium in vertebra (highly trabecular bone), rib (a mixture of trabecular and cortical bone), and long bone shafts (highly cortical bone) from skeletal remains of three human donors. Respective mean activity concentrations in vertebra, rib, and long bone shaft were 0.063, 0.083, and 0.044 Bq/kg (1.70, 2.24, and 1.19 pCi/kg) for ^{230}Th, and 0.048, 0.045, and 0.030 Bq/kg (1.30, 1.22, and 0.81 pCi/kg) for ^{232}Th.

Kumar et al. (2009) studied the distribution of thorium in the brains of female Swiss albino mice following intraperitoneal exposure of eight animals for 30 days to 4.1 mg thorium/kg/day as thorium nitrate pentahydrate. Thorium distributed nonuniformly within the brain following the order: cerebellum (1.2%) > cortex (0.8%) > hippocampus (0.66%) > striatum (0.4%).

Inhalation Exposure. The median concentrations of ^{232}Th, ^{230}Th, and ^{228}Th in bone and various soft tissues of autopsy samples of a control population from Grand Junction, Colorado, and Washington, DC are presented in Table 3-1 (Ibrahim et al. 1983; Wrenn et al. 1981; Singh et al. 1983). The maximum concentration of all three thorium isotopes was found in the tracheobronchial lymph nodes, with lungs

Table 3-1. The Median Concentrations of Thorium Isotopes in Autopsy Samples from Grand Junction, Colorado, and Washington, DC (in pCi/kg Wet Weight)

Organ	Number of samples analyzed	Grand Junction, Colorado			Number of samples analyzed	Washington, DC		
		^{228}Th	^{230}Th	^{232}Th		^{228}Th	^{230}Th	^{232}Th
Lung	19	0.28	0.84	0.58	10	0.24	0.31	0.32
Lymph node	14	5.1	11.0	7.8	10	2.6	4.6	2.8
Liver	16	0.07	0.15	0.03	10	0.09	0.15	0.05
Kidney	17	0.07	0.29	0.07	8	0.09	0.17	0.03
Bone	16	0.54	0.92	0.16	7	0.66	0.32	0.1
Testicles	44	0.02	0.06	0.05	–	–	–	–
Spleen	14	0.06	0.13	0.09	–	–	–	–
Thyroid	1	0.33	0.82	0.65	–	–	–	–

Sources: Ibrahim et al. 1983; Singh et al. 1983; Wrenn et al. 1981

and bones containing the next highest activity of thorium isotopes. The high activity in the lymph nodes implies that some of the thorium is cleared from the lungs by the lymphatic system and deposited in the lymph nodes (Mausner 1982; Wrenn et al. 1981).

One possible explanation for the higher activity of ^{228}Th than ^{232}Th in bone is that a major portion of the ^{228}Th may be from intake of ^{228}Ra (radium appears to be absorbed from the gastrointestinal tract to a greater extent than thorium); ^{228}Ra concentrates in bones and decays to ^{228}Th (Wrenn et al. 1981).

The dose rates to various organs in humans from environmental thorium were estimated to be 2.2–4.5, 0.41–0.44, 0.19–0.23, 0.057–0.071, and 0.071–0.072 mrad/year in the lymph nodes, bone, lungs, liver, and kidneys, respectively (Wrenn et al. 1981). The dose rates to organs tended to be higher in subjects living in the vicinity of uranium mine tailings, and the dose rates to the organs in miners were even higher (4.8–10.5 mrad/year in the lymph nodes and 1.2–1.5 mrad/year in the lungs) (Wrenn et al. 1981).

Chen et al. (2003) estimated average thorium lung burdens of 1.60 Bq (43.24 pCi) in a group of 638 rare-earth miners in China who were considered to have experienced occupational exposure to thorium dust; an average thorium lung burden of 0.30 Bq (8.11 pCi) was estimated for a group of 143 workers at the same mine who were classified as not exposed to thorium dust. The estimates of lung burdens were based on measurements of exhaled thoron (^{220}Rn) activity.

Jaiswal et al. (2004) assessed thorium lung burden and total body thorium content in five workers employed for 10–32 years in a plant that processed thorium concentrate. Average thorium activity measured in various departments of the plant was generally <0.12 Bq/m^3 (3.24 pCi/m^3). Lung and whole-body thorium contents were estimated from results of *in vivo* gamma counting of actinium-228 (^{228}Ac) and thallium-208 (^{208}Tl); limits of detection for thorium in the thoracic area and whole body were 12 and 52 Bq (324.32 and 1,405.41 pCi), respectively. Measured thorium lung burden ranged from 15 to 67 Bq (405.41–1,810.81 pCi); total body thorium content ranged from <52 to 168 Bq (<1,405.41–4,540.54 pCi).

Hewson and Fardy (1993) reported blood and urine thorium concentrations ranging from 170 to 2,000 ng/L (geometric mean 480 ng/L; geometric standard deviation [GSD] 1.7, n=25) in the serum and 3–210 ng/L (geometric mean 31 ng/L, n=32) in the urine of mineral sands workers in Western Australia. The geometric means of unexposed workers were 320 ng/L for serum and 5 ng/L for urine. Based on periodically-recorded data regarding alpha radioactivity in the workplace air and historical worker data, the study authors calculated a geometric mean ^{232}Th intake of 0.4 Bq/day (10.81 pCi/day) and geometric

mean exposure time period of 1,597 days for the 25 workers. Neither serum nor urine concentrations correlated with cumulative exposures, but serum levels were less variable and considered to be a more reliable indicator of exposure.

Stehney (1999) measured ^{232}Th concentrations in human autopsy tissue samples from four thorium mill workers, including a millwright and three laborers. Those values were used to compare two predictive dosimetry models (one based on ICRP Report No. 30, the other based on ICRP Report No. 68 and 69), and the latter was found to be more accurate. Stehney and Lucas (2000) later reported additional analytical results for the same four workers and an additional laborer. The ^{232}Th concentrations (in mBq per g wet tissue) were 0.009–0.068 for kidneys, 0.015–0.68 for liver, 0.14–1.19 for bones, 0.97–5.8 for spleen, 0.17–79 for lungs, and 3.9–1,210 for pulmonary lymph nodes (0.24–1.84 pCi/g for kidneys, 0.405–18.38 pCi/g for liver, 3.78–32.16 pCi/g for bones, 26.22–156.76 pCi/g for spleen, 4.59–21.35 pCi/g for lungs, and 105.41–32,702.70 pCi/g for pulmonary lymph nodes). Distribution was higher in lower portions of the lung (possibly due to settling) and higher in vertebrae than in other bones. Lung levels remained high for decades after exposure ended, indicating that actinides were retained with a much longer half-time than the 500 days recommended by ICRP Publication No. 30, but results were not sufficient to recommend a new value. After extended periods, the fractions of thorium remaining in bone, liver, and lungs were comparable between workers and the general population.

Hall et al. (1951) exposed rats and rabbits by inhalation to various thorium compounds for 6 hours/day, 5 days/week. For rats, a trend was noted for increasing deposition with length of exposure, with 11.4 mg/m^3 of thorium tetrafluoride producing femur concentrations of 3.1, 6.1, 4.3, and 8.9 µg thorium/g femur at 1, 2, 3, and 4 weeks of exposure, respectively. Rats exposed to 28 mg/m^3 of thorium oxalate for 4 weeks resulted lung, femur, spleen, and liver concentrations of 126, 5.2, <1.5, and 0.64 µg thorium/g tissue, respectively. This deposition trend held for rabbits, but with a 4-fold smaller relative lung burden.

Hodge et al. (1960) repeatedly exposed dogs to thorium dioxide dust at 5 mg/m^3 (0.55 nCi/m^3) for 1 year. At 6–7 years following cessation of exposures, thorium was found in lung and pulmonary lymph nodes at wet tissue concentrations of 0.84 and 37 mg/g, respectively (ratio of thorium levels in lung:pulmonary lymph nodes = 1:44). These results demonstrate distribution of insoluble thorium dioxide to pulmonary lymph nodes and long-term retention in both lung and pulmonary lymph nodes.

Oral Exposure. Autopsy data of persons environmentally exposed to thorium indicated that pulmonary lymph nodes contained the highest levels of thorium (mean 53.4 µg/kg), followed by the lungs (mean of

5.4 µg/kg, ranging from 1.5 to 16 µg/kg) and bones (mean of 0.55 µg/kg, ranging from 0.2 to 9.0 µg/kg) (Sunta et al. 1987). This study estimated that the daily intake of thorium through food, water, and inhalation was 2.29 µg/day, with the majority from food and water ingestion (2.27 µg/kg). However, it was determined that, since absorption through the gastrointestinal tract is low (0.02%), two-thirds of the body burden of thorium results from inhalation exposure.

Neonatal rats retained 50% of the absorbed amount of thorium (1.1% of the administered amount) in the skeleton (Sullivan et al. 1983). In the same study, adult mice retained 75% of the absorbed amount of thorium (0.065% of the administered amount) in the skeleton. Traikovich (1970) found that about 75% of the absorbed amount (0.5% of the administered amount) of ^{232}Th (as thorium nitrate) was located in the bones of rats.

Dermal Exposure. No studies were located regarding the rate and extent of distribution of thorium following dermal exposure of humans or animals.

Other Routes of Exposure. Maletskos et al. (1969) found that, following intravenous injection in humans, ^{234}Th from thorium citrate generally was retained in the skeleton and soft tissues rather than in the RES, as found with Thorotrast. Studies in mice also demonstrated that intraperitoneally-injected ^{227}Th distributes directly to bone (Müller et al. 1978). A similar distribution pattern was found in dogs injected intravenously with ^{228}Th as thorium citrate (Stover et al. 1960). Intravenous exposure studies in rats and guinea pigs, however, showed a distribution of ^{234}Th (from thorium sulfate) similar to Thorotrast: 60–68% in the liver, 3–7% in the spleen, 0.4–l% in the kidneys, and about 10% in the remaining carcass, including bone (Scott et al. 1952). Peter-Witt and Volf (1985) determined that the mass of ^{234}Th intravenously injected (carrier-free) in rats dictated the pattern of distribution. A "critical" concentration of thorium in the extracellular space was found to be between 10^{-7} and 10^{-6} M; above this concentration, thorium hydrolyzes, becomes colloidal, and distributes primarily to organs of the reticuloendothelial system; below this concentration, thorium is distributed primarily to bone. The exposure levels in the human and animal studies cannot be compared since the concentration injected was not reported in the human study.

Kumar et al. (2012) assessed the distribution of thorium in liver and blood of rats injected intramuscularly with 0.6 mg thorium/kg as thorium nitrate. After 24 hours, 42% of the thorium was in retained the liver and 11% was in the blood.

3.1.3 Metabolism

Transferrin plays a major role in the transport and cellular uptake of thorium (Peter and Lehmann 1981). Thorium can be displaced from transferrin by an excess of iron, but it is not known whether thorium and iron bind to the same sites on the transferrin molecule.

Jeanson et al. (2010) assessed the pH-dependence of thorium binding to transferrin *in vitro*. They reported that Th(IV) (unlike tetravalent plutonium and neptunium) was never completely complexed to transferrin over the pH range studied, and especially below pH 7. They suggested that a relatively large ionic size, coupled with a relatively weak hydrolysis constant, allows thorium to be easily displaced from transferrin or blocked from interaction. This is consistent with the transferrin pH cycle.

3.1.4 Excretion

Inhalation Exposure. After inhalation exposure, the primary route of excretion is in the feces following ciliary clearance from the lungs to the gastrointestinal tract (Wrenn et al. 1981). Fecal excretion may account for as much as 97% of total excretion (Fisher et al. 1983). Higher levels of ^{230}Th were excreted in the feces by active crushermen (uranium mill workers exposed to uranium ore dust in the crusher building) compared to retired workers or controls (Fisher et al. 1983). Levels of ^{230}Th in the urine were comparable to those of retired workers, and the levels in both were significantly greater than controls.

The biological half-lives of ^{232}Th and ^{230}Th in the lungs of subjects living in the vicinity of uranium mine tailings (Grand Junction, Colorado) were 5.3 and 1.4 years, respectively. The biological half-lives for subjects in a non-mine area (Washington, DC) were 2.6 and 1.0 years for ^{232}Th and ^{230}Th, respectively (Wrenn et al. 1981). Since biological half-lives in humans should be the same regardless of where people live, the differences at the two locations may reflect the duration of exposure, the time between exposure and sampling, or the inhalation of larger particle size dust in Grand Junction compared to Washington, DC. The ^{232}Th from nature apparently is retained in the lungs longer than the ^{230}Th.

In a subject who had accidentally inhaled ^{228}Th (alpha emitter, radioactive half-life of 1.9 years) as thorium dioxide, the biological half-life for long-term clearance of ^{228}Th from the body was at least 14 years as a result of skeletal deposition (Newton et al. 1981). The early lung clearance of ^{228}Th was found to be on the order of approximately 50 days, thereby designating thorium dioxide a class W compound (biological half-life in weeks) as opposed to the class Y (biological half-life in years) designation recommended by ICRP (1979). Classes D, W, and Y (days, weeks, and years) have been

redesignated as classes F, M, and S (fast, medium, and slow). Davis (1985), however, concluded that both ^{232}Th (as thorium nitrate) and $^{232}ThO_2$ were class Y compounds by determining the solubility in simulated lung fluid. The near equilibrium of ^{230}Th, ^{234}U, and ^{238}U in the lungs of former uranium miners suggests that the elimination rates of these nuclides are similar (Singh et al. 1987; Wrenn et al. 1985). In dogs, the ^{230}Th/^{234}U ratio increases with time, suggesting that uranium is cleared faster than thorium from dog lungs (Singh et al. 1986). An effective half-life of about 10 days in the lungs of rats was reported for ^{227}Th inhaled as thorium nitrate (radioactive half-life of 18.7 days and biological half-life of about 20 days) (Müller et al. 1975). Pavlovskaia et al. (1974a) determined that the excretion of intratracheally-administered ^{228}Th (as thorium dioxide or thorium chloride) in the feces occurred in two phases in the rat: in the first phase, up to 60% of the ^{228}Th contained in the body was eliminated, and in the second phase, the rate of ^{228}Th excretion in the feces averaged 0.25% of the body burden daily.

Hewson and Fardy (1993) reported thorium concentrations ranging from 3 to 210 ng/L (geometric mean 31 ng/L; GSD 2.6) in the urine of 34 mineral sands workers in Western Australia. It was estimated that urinary excretion averaged 2.5% of the thorium body burden. Based on periodically-recorded data regarding alpha radioactivity in the workplace air and historical worker data, the study authors calculated a geometric mean ^{232}Th intake of 0.40 Bq/day (10.81 pCi/day) and geometric mean exposure time period of 1,383 days for these 34 workers. However, neither urine nor serum concentration related to either the period of employment or cumulative exposure.

Terry et al. (1995) assessed the fecal excretion of thorium in two workers exposed to thorium in the monazite section of a mineral sands dry separation plant over a 5-day work period followed by a 5-day work period without exposure to thorium dust. The workers had been isolated from airborne radioactive dust for at least 7 days prior to the monitoring period. For the 5-day exposure period, one worker wore an air sampler and the other a cascade impactor. Exposures totaled 26.4 Bq (713.51 pCi) of 14 μm atmospheric median aerodynamic diameter (AMAD) dust particles. For both workers, peak thorium fecal excretion occurred on day 6 (the day after the end of the 5-day exposure period). The rapid excretion following exposure indicated that fecal sampling can be used to assess acute exposures to thorium. During the 10-day monitoring period, fecal excretion was 970 μg thorium for one worker and 1,980 μg thorium for the other worker. The 2-fold difference was unexpected and speculated to be due to mouth breathing versus nose breathing.

Jaiswal et al. (2004) measured thorium activity in the lungs, total body, and daily urine of five workers employed for 10–32 years in a plant that processed thorium hydroxide concentrate and exposed primarily

by the inhalation route. The lung activity measured for each individual (15–67 Bq; 405.41–1,810.81 pCi) was used to estimate their total body content and daily urine excretion. Those values were compared with measured total body content (<52–168 Bq; <1,405.41–4,540.54 pCi) and daily urinary activity (0.46–1.84 mBq; 12.43–49.73 pCi). Measured and calculated results compared more favorably when using the combined ICRP human respiratory tract model (ICRP 1994b) and ICRP biokinetic model (ICRP 1995) than with the older biokinetic model (ICRP 1979).

Oral Exposure. It was determined in several species of animals (mice, rats, rabbits) that >95% of the ingested amount is excreted in the feces within several days (approximately 2–4 days) (Patrick and Cross 1948; Scott et al. 1952; Sollmann and Brown 1907). Sollmann and Brown (1907) concluded that, since very little thorium was excreted in the feces following intravenous or intramuscular injection, and since very little thorium was excreted in the urine following ingestion, appreciable amounts of thorium were neither absorbed nor excreted from the gastrointestinal tract.

Dermal Exposure. No studies were located regarding the rate and extent of excretion of thorium following dermal exposure of humans or animals.

Other Routes of Exposure. In contrast to the thorium from Thorotrast (a thorium dioxide and dextran suspension) after intravenous injection, a higher percentage of thorium from more soluble thorium compounds is excreted. Following intravenous injection of ^{234}Th (as thorium citrate) in humans, there is a relatively rapid but small (7%) amount of excretion within the first 20 days. A urine/feces ratio of 12 for male subjects and 24 for female subjects was determined. About 93% of the injected ^{234}Th was retained at 100 days after injection, with a biological half-time of >5 years (Maletskos et al. 1969).

Less than 5% of thorium was excreted in the urine up to 42 days after intravenous injection of ^{234}Th (as thorium sulfate) in rats and guinea pigs (Scott et al. 1952). After intravenous injection, the amount of thorium excreted in the feces was 0.7–24.5% of the level administered for 14–42 days in rats, 0.6 and 14.6% for 2 and 5 days in guinea pigs, and 0.9% for 7 days in rabbits. In dogs injected with ^{228}Th (as thorium citrate), urinary excretion dominated initially, but after 2.5 years, the fecal to urinary ratio approximated 1.0 (Stover 1981; Stover et al. 1960). Thomas et al. (1963) reported the excretion of thorium citrate administered as ^{234}Th tracer plus ^{232}Th carrier in rats. No differences were found in the rate or route of excretion following various routes of administration (intravenous, intraperitoneal, intratracheal, and intramuscular). In the first 2 days, 25–30% of the thorium was excreted. Most of the thorium was excreted in the feces and not in the urine. At a high exposure level, the feces/urine ratio was

45 and at a low level, it was 1.6. This indicates that at the high level, thorium was hydrolyzed, became insoluble, was taken up by the RES, and was quickly cleared from the blood. The higher fecal levels of thorium in the high exposure level animals suggest greater biliary excretion.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

The ICRP developed a Human Respiratory Tract Model (HRTM) for Radiological Protection, which contains respiratory tract deposition and clearance compartmental models for inhalation exposure that may be applied to thorium (ICRP 1994b, 1996). The ICRP also developed a biokinetic model for human oral exposure that applies to thorium (ICRP 1995). Several more recent enhancements to the oral exposure model have been reported. A multicompartmental gastrointestinal tract model was developed to replace what was originally a single parameter model (Human Alimentary Tract Model, HATM) (ICRP 2006). A hair compartment was developed to support biomonitoring of ingestion intakes (e.g., drinking water exposures) (Li et al. 2009). Drinking water and dietary exposure models and Bayesian approaches have been developed to improve thorium dose assessments made with the ICRP model (Little et al. 2003, 2007). The National Council on Radiation Protection and Measurements (NCRP) has also developed a respiratory tract and biokinetics model for inhaled radionuclides (NCRP 1997).

Human Respiratory Tract Model for Radiological Protection (ICRP 1994b, 1996)

Deposition. The ICRP developed a deposition model for behavior of aerosols and vapors in the respiratory tract. It was developed to estimate the fractions of radioactivity in breathing air that are deposited in each anatomical region. ICRP provides inhalation dose coefficients that can be used to estimate the committed equivalent and effective doses to organs and tissues throughout the body based on a unit intake of radioactive material. The model applies to three levels of particle solubility and a wide

range of particle sizes (approximately 0.0005–100 μm in diameter), and parameter values can be adjusted for various segments of the population (e.g., sex, age, level of physical exertion). This model also allows one to evaluate the bounds of uncertainty in deposition estimates. Uncertainties arise from natural biological variability among individuals and the need to interpret some experimental evidence that remains inconclusive. It is applicable to particles containing uranium, but was developed for a wide variety of radionuclides and their chemical forms.

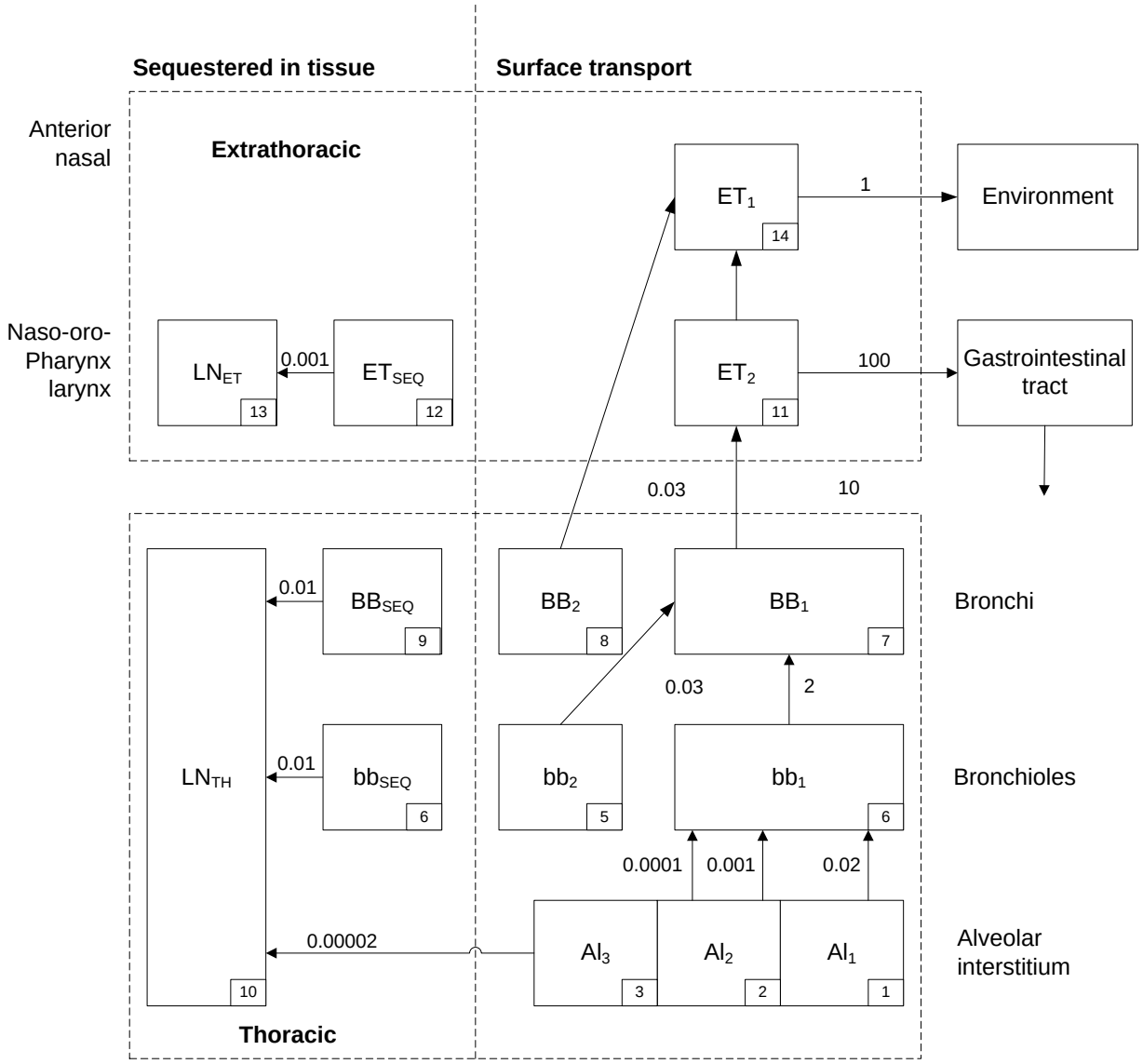
The ICRP deposition model estimates the amount of inhaled material that initially enters each compartment (see Figure 3-1). The model was developed with five compartments: (1) the anterior nasal passages (ET1); (2) all other extrathoracic airways (ET2) (posterior nasal passages, the nasopharynx and oropharynx, and the larynx); (3) the bronchi (BB); (4) the bronchioles (bb); and (5) the alveolar interstitium (AI). Particles deposited in each of the regions may be removed from each region and redistributed either upward into the respiratory tree or to the lymphatic system and blood by different particle removal mechanisms.

For extrathoracic deposition, the model uses experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. Similarly to the extrathoracic region, experimental data served as the basis for lung (bronchi, bronchioles, and alveoli) aerosol transport and deposition. A theoretical model of gas transport and particle deposition was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 3-2 provides reference respiratory values for the general Caucasian population under several levels of activity.

Respiratory Tract Clearance. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various radioactive materials.

Figure 3-2 presents the compartmental model and is linked to the deposition model (Figure 3-1) and to reference values presented in Table 3-3. Table 3-3 provides clearance rates and deposition fractions for each compartment for insoluble particles. The table provides rates of insoluble particle transport for each of the compartments, expressed as a fraction per day and also as half-time. ICRP also developed modifying factors for some of the parameters, such as age, smoking, and disease status. Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

Figure 3-1. Respiratory Tract Compartments in Which Particles May be Deposited*



*Compartment numbers shown in lower right corners are used to define clearance pathways. The clearance rates, half-lives, and fractions by compartment, as well as the compartment abbreviations, are presented in

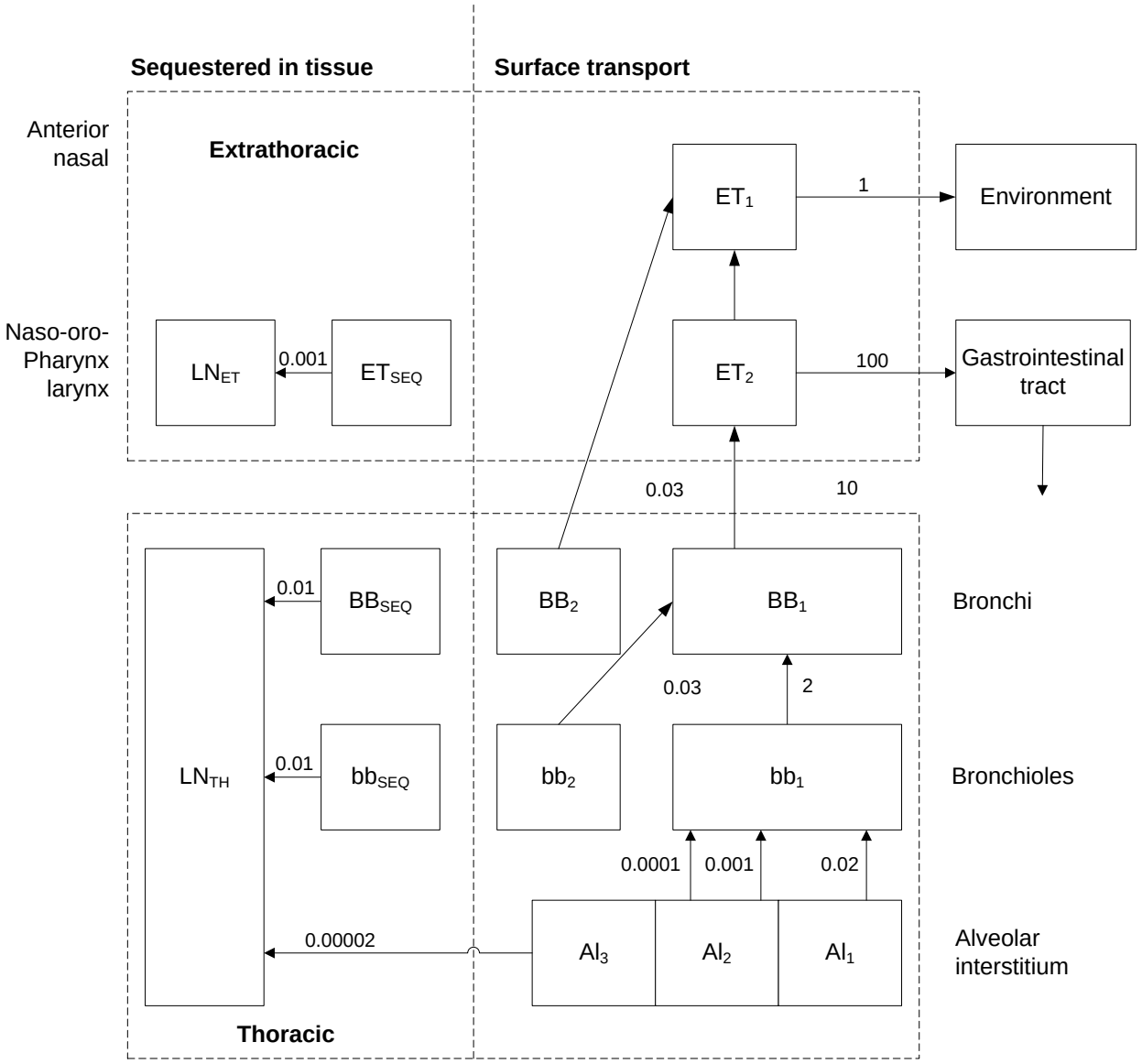
Table 3-2. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity

Breathing parameters:	3 Months	1 Year	5 Years	10 Years			15 Years		Adult	
				Male	Female	Both	Male	Female	Male	Female
Resting (sleeping); maximal workload 8%										
Breathing parameters:										
V_T (L)	0.04	0.07	0.17	–	–	0.3	0.5	0.417	0.625	0.444
B ($m^3 hour^{-1}$)	0.09	0.15	0.24	–	–	0.31	0.42	0.35	0.45	0.32
f_R ($minute^{-1}$)	38	34	23	–	–	17	14	14	12	12
Sitting awake; maximal workload 12%										
Breathing parameters:										
V_T (L)	NA	0.1	0.21	–	–	0.33	0.533	0.417	0.75	0.464
B ($m^3 hour^{-1}$)	NA	0.22	0.32	–	–	0.38	0.48	0.4	0.54	0.39
f_R ($minute^{-1}$)	NA	36	25	–	–	19	15	16	12	14
Light exercise; maximal workload 32%										
Breathing parameters:										
V_T (L)	0.07	0.13	0.24	–	–	0.58	1.0	0.903	1.25	0.992
B ($m^3 hour^{-1}$)	0.19	0.35	0.57	–	–	1.12	1.38	1.3	1.5	1.25
f_R ($minute^{-1}$)	48	46	39	–	–	32	23	24	20	21
Heavy exercise; maximal workload 64%										
Breathing parameters:										
V_T (L)	NA	NA	NA	0.841	0.667	–	1.352	1.127	1.923	1.364
B ($m^3 hour^{-1}$)	NA	NA	NA	2.22	1.84	–	2.92	2.57	3.0	2.7
f_R ($minute^{-1}$)	NA	NA	NA	44	46	–	36	38	26	33

B = ventilation rate; f_R = respiration frequency; NA = not applicable; V_T = tidal volume

Source: See Annex B (ICRP 1994b) for data from which these reference values were derived.

Figure 3-2. Environmental Pathways for Potential Human Health Effects from Thorium*



*See Table 3-3 for rates, half-lives, and fractions by compartment.

Source: ICRP 1994b

Table 3-3. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A				
Clearance rates for insoluble particles				
Pathway	From	To	Rate (d^{-1})	Half-life[a]
$m_{1,4}$	AI_1	bb_1	0.02	35 days
$m_{2,4}$	AI_2	bb_1	0.001	700 days
$m_{3,4}$	AI_3	bb_1	$1x10^{-4}$	7,000 days
$m_{3,10}$	AI_3	LN_{TH}	$2x10^{-5}$	No data
$m_{4,7}$	bb_1	BB_1	2	8 hours
$m_{5,7}$	bb_2	BB_1	0.03	23 days
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 days
$m_{7,11}$	BB_1	ET_2	10	100 minutes
$m_{8,11}$	BB_2	ET_2	0.03	23 days
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 days
$m_{11,15}$	ET_2	GI tract	100	10 minutes
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 days
$m_{14,16}$	ET_1	Environment	1	17 hours

Table 3-3. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part B		
Partition of deposit in each region between compartments[b]		
Region or deposition site	Compartment	Fraction of deposit in region assigned to compartment[c]
ET_2	ET_2	0.9995
	ET_{seq}	0.0005
BB	BB_1	0.993-f_s
	BB_2	f_s
	BB_{seq}	0.007
Bb	bb_1	0.993-f_s
	bb_2	f_s
	bb_{seq}	0.007
AI	AI_1	0.3
	AI_2	0.6
	AI_3	0.1

[a]The half-lives are approximate since the reference values are specified for the particle transport rates and are rounded in units of days^{-1}. A half-life is not given for the transport rate from AI_3 to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-life of compartment AI_3 is determined by the sum of the clearance rates.
[b]See paragraph 181, Chapter 5 (ICRP 1994b) for default values used for relating f_s to d_{ae}.
[c]It is assumed that fs is size-dependent. For modeling purposes, f_s is taken to be:

$$f_s = 0.5 \text{ for } d_{ae} \leq 2.5\sqrt{(\rho/x)}\ \mu m \text{ and}$$

$$f_s = 0.5e^{0.63(d_{ae}\sqrt{(\rho/x)}-2.5)} \text{ for } d_{ae} > 2.5\sqrt{(\rho/x)}\ \mu m$$

where
f_s = fraction subject to slow clearance
d_{ae} = aerodynamic particle diameter/(μm)
ρ = particle density (g/cm^3)
χ = particle shape factor

AI = alveolar-interstitial region; BB = bronchial region; bb = bronchiolar region; BB_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchial region; bb_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchiolar region; ET = extrathoracic region; ET_{seq} = compartment representing prolonged retention in airway tissue of small fraction of particles deposited in the nasal passages; GI = gastrointestinal; LN_{ET} = lymphatics and lymph nodes that drain the extrathoracic region; LN_{TH} = lymphatics and lymph nodes that drain the thoracic region

Source: ICRP 1994b

The clearance of particles from the respiratory tract is a dynamic process. The rate of clearance generally changes with time from each region and by each route. Following deposition of large numbers of particles (acute exposure), transport rates change as particles are cleared from the various regions. Physical and chemical properties of deposited material determine the rate of dissolution and as particles dissolve, absorption rates tend to change over time. By creating a model with compartments of different clearance rates within each region (e.g., BB1, BB2, BBseq), the ICRP model overcomes problems associated with time-dependent functions. Each compartment clears to other compartments by constant rates for each pathway.

Particle transport from all regions is toward both the lymph nodes and the pharynx, and a majority of deposited particles end up being swallowed. In the front part of the nasal passages (ET1), nose blowing, sneezing, and wiping remove most of the deposited particles. Particles remain here for about a day. For particles with activity median aerodynamic diameters (AMADs) a few micrometers or greater, the ET1 compartment is probably the largest deposition site. A majority of particles deposited at the back of the nasal passages and in the larynx (ET2) are removed quickly by the fluids that cover the airways. In this region, particle clearance is completed within 15 minutes.

Ciliary action removes deposited particles from both the bronchi and bronchioles. Though it is generally thought that mucociliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles are cleared more slowly. Evidence for this is found in human studies. For humans, retention of particles deposited in the lungs (BB and bb) is apparently biphasic. The “slow” action of the cilia may remove as many as half of the bronchi- and bronchiole-deposited particles. In human bronchi and bronchiole regions, mucus moves more slowly the closer to the alveoli it is. For the faster compartment, it has been estimated that it takes about 2 days for particles to travel from the bronchioles to the bronchi and 10 days from the bronchi to the pharynx. The second (slower) compartment is assumed to have approximately equal fractions deposited between BB2 and bb2 and both with clearance half-times estimated at 20 days. Particle size is a primary determinant of the fraction deposited in this slow thoracic compartment. A small fraction of particles deposited in the BB and bb regions is retained in the airway wall for even longer periods (BBseq and bbseq).

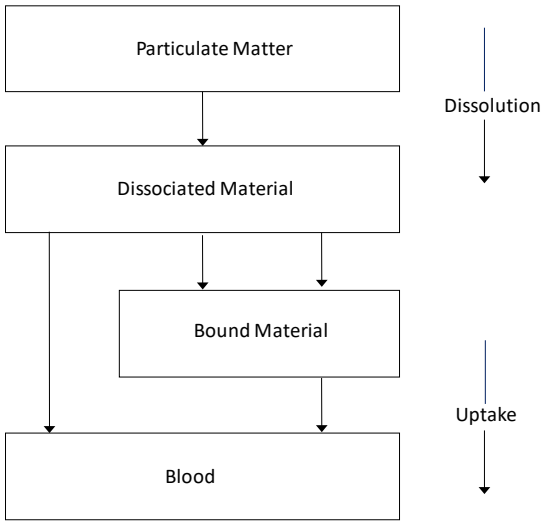
If particles reach and become deposited in the alveoli, they tend to stay imbedded in the fluid on the alveolar surface or move into the lymph nodes. The one mechanism by which particles are physically resuspended and removed from the AI region is coughing. For modeling purposes, the AI region is divided into three subcompartments to represent different clearance rates, all of which are slow. In the

alveolar-interstitial region, human lung clearance has been measured. The ICRP model uses 2 half-times to represent clearance: about 30% of the particles have a 30-day half-time and the remaining 70% are given a half-time of several hundred days. Over time, AI particle transport falls and some compounds have been found in lungs 10–50 years after exposure.

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET1), where no absorption occurs. It is essentially a two-stage process, as shown in Figure 3-3. First, there is a dissociation (dissolution) of particles, then the dissolved molecules or ions diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of specific data for specific compounds, the model uses the following default absorption rate values for those specific compounds that are classified as Types F (fast), M (medium), and S (slow):

- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions, and 50% of material deposited in ET2. Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET and 50% for mouth breathing. No thorium compounds are assigned as type F; however, thorium nitrate might behave in this manner under some circumstances.
- For Type M, about 70% of the deposit in AI reaches the blood eventually. There is rapid absorption of about 10% of the deposit in BB and bb, and 5% of material deposited in ET2. Thus, there is rapid absorption of approximately 2.5% of the deposit in ET for nose breathing, and 5% for mouth breathing. Type M thorium compounds include nitrate and all other compounds than oxides, and hydroxides.
- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually. Type S thorium compounds include oxides and hydroxides.

Figure 3-3. The Human Respiratory Tract Model: Absorption into Blood

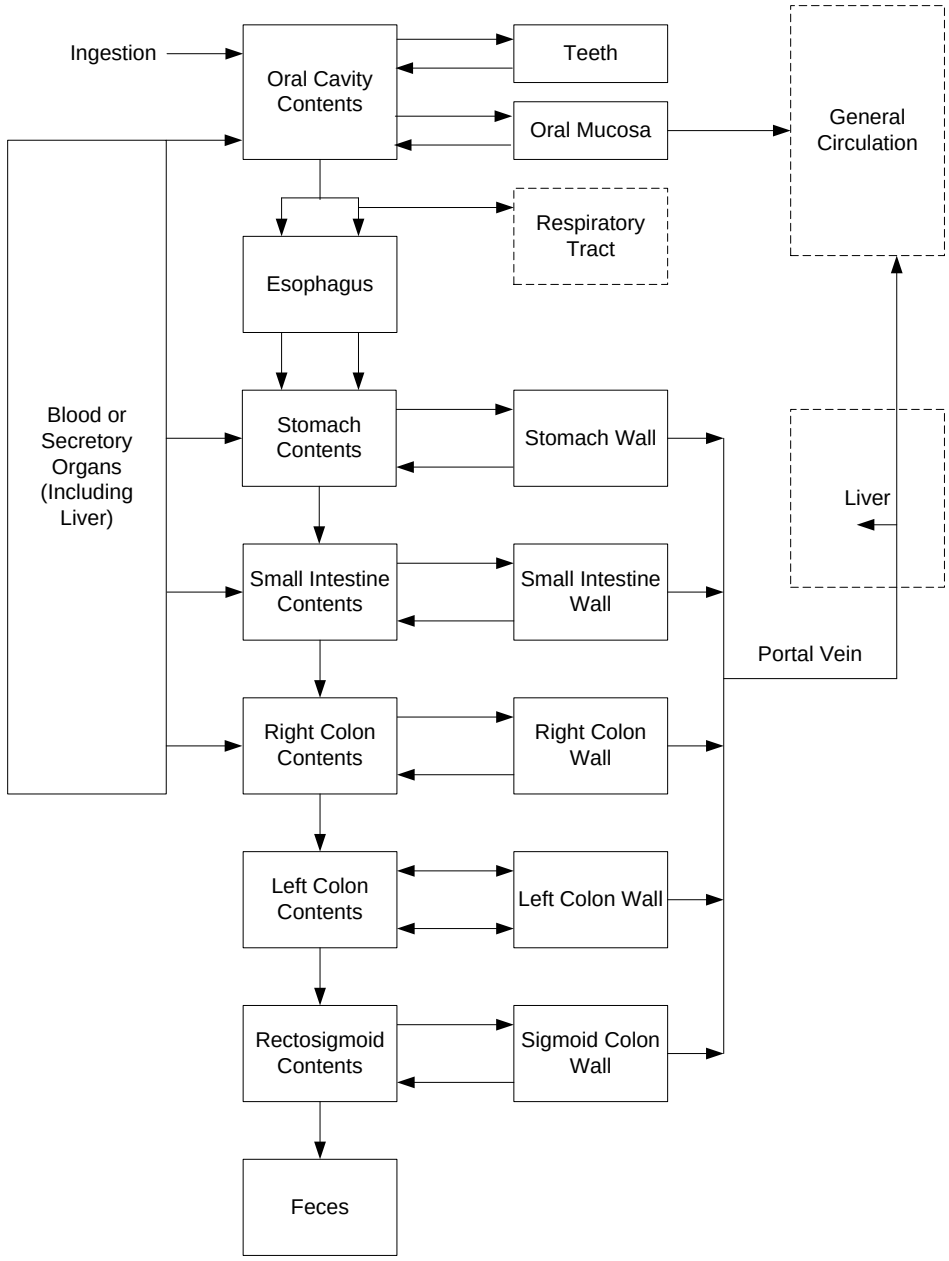


Human Alimentary Tract Model for Radiological Protection (ICRP 2006)

The ICRP HATM is a generic multicompartment gastrointestinal tract model that was developed for applications to radiation risk assessments of radionuclides. The model replaced an earlier gastrointestinal absorption model that consisted of single compartment and single parameter representation of absorption of radionuclides into the central plasma compartment from the small intestine. The structure of the multicompartment model is shown in Figure 3-4. The model simulates the following major processes that can contribute to absorption of radionuclides from the gastrointestinal tract as well as contact and retention of radionuclides in the gastrointestinal tract tissues (i.e., which could contribute to radiation dose to these tissues):

- Entry of a radionuclide into the mouth by ingestion, or into the esophagus after mechanical clearance from the respiratory tract; sequential transfer of the radionuclide through the contents of the oral cavity, esophagus, stomach, small intestine, and segments of the colon, followed by excretion in feces.
- 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 and intestines.
- Transfer from the oral mucosa or walls of the stomach and intestines back into the luminal contents or into blood (absorption).
- Transfer from various secretary organs or blood into the contents of certain segments of the alimentary tract (secretion).

Figure 3-4. Structure of the Human Alimentary Tract Model (HATM)



ICRP (1995) developed a compartmental model of the kinetics of ingested thorium in humans that is directly applicable to adults and contains conservative assumptions for applicability to 3-month-old infants; 1-, 5-, and 10-year-old children, and 15-year-old adolescents. The model is a revision of an earlier ICRP biokinetic model of thorium (ICRP 1979). Thorium in blood distributes to the skeleton, liver, kidneys, gonads, and gastrointestinal tract. Excretion pathways included in the model are kidney to urine and feces. The model has been evaluated with human data on thorium lung retention and urinary excretion and postmortem thorium tissue levels in workers exposed to airborne thorium or members of the general population without known occupational exposure to thorium (Jaiswal et al. 2004; Li et al. 2007; Roth et al. 2005; Stehney 1999; Terry and Hewson 1995; Terry et al. 1995). The model has also been evaluated using measured biokinetic data from rats following intratracheal instillation of thorium compounds (Hodgson et al. 2003; Stradling et al. 2001). The model has been used to establish the radiation dose (Sv) per unit of ingested or inhaled thorium (Bq) for intake ages 3 months to adult (ICRP 1995, 2001). The dose integration period is 50 years for acute intake at age 25 years. The model is designed to calculate radiation dose coefficients (Sv/Bq) corresponding to specific inhalation or ingestion exposures to thorium isotopes. Dose coefficients have been estimated for all major organs, including the bone surfaces, bone marrow, and liver, and other tissues (ICRP 1995, 1996). The model is based on both human and animal data for thorium; however, it might not reflect the distribution of injected Thorotrast due to its colloidal chemistry. However, it is intended for applications to human dosimetry. Applications to other species would require consideration of species-specific adjustments in model parameters.

3.1.6 Animal-to-Human Extrapolations

No data were located regarding species-specific differences in the toxicokinetics or toxicity of thorium compounds. The toxicity of thorium is generally considered to be radiological in nature, but may include chemical toxicity. Adverse health effects associated with relatively low-level thorium exposure for short durations might not be expected to be radiation induced.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to thorium are discussed in Section 5.7, Populations with Potentially High Exposures.

Limited information was located regarding populations with increased susceptibility to thorium.

Gonzalez-Vasconcellos et al. (2011) evaluated mice with Rb1 tumor suppressor gene and p16 germline defects to identify their impact on osteosarcomagenesis induced by thorium. Female mice (n=42–80) in each of three strains were injected with 185 Bq/g (~5,000 nCi/kg) of ^{227}Th, tumors were assessed over >400 days, and DNA of healthy and tumor tissues was assessed for the allelic ratio of Rb1 to p16 loci. Rb1 germline defects resulted in an increased predisposition for thorium-induced osteosarcoma. However, a p16 defect tends to shorten tumor latency, in the later stages of tumor promotion, rather than affecting susceptibility.

Neonatal animals have been found to absorb 20–40 times more thorium through the gastrointestinal tract than adult animals (Sullivan 1980a, 1980b; Sullivan et al. 1983), indicating that children may be more susceptible than adults to the effects of thorium. In contrast, LD_{50} values of 800–1,100 and 513 mg thorium/kg were reported for weanling and mature rats, respectively, exposed to thorium nitrate once via intraperitoneal injection, indicating that the mature rats were more susceptible than the weanlings to thorium lethality.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment

of an organism (NAS/NRC 1989). Biomarkers of exposure for a radionuclide can include radioactive decay products if they are measurable within a compartment. The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to thorium are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for thorium from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by thorium are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Exposure to thorium can be determined by measurement of radioactive thorium and/or daughters (e.g., ^{220}Rn, ^{222}Rn) in the feces, urine, and expired air. The primary route of excretion of thorium is in the feces following either inhalation or oral exposure. Fecal excretion is essentially complete in a matter of several days (Patrick and Cross 1948; Scott et al. 1952; Sollman and Brown 1907; Wrenn et al. 1981). The measurement of external gamma rays emitted from thorium daughters present in the subject's body and of thoron (^{222}Rn) in the expired air many years following exposure can be used to estimate the body burden of thorium (Conibear 1983).

No tissue concentrations in humans were found that correlated with health effects, but about 20 pCi was found in the lungs of an exposed worker suffering from lung fibrosis. However, it was not clear if the fibrosis was due to thorium, or to rare-earth-containing fumes and dusts (Vocaturo et al. 1983).

Blood levels of thorium following oral exposure of humans to simulated radium dial paint demonstrated that approximately 0.02% of the ingested amount was absorbed by the gastrointestinal tract (Maletskos et al. 1969). This study was the basis for the ICRP (1979) recommendation of an oral absorption factor of 0.02% for thorium.

3.3.2 Biomarkers of Effect

Occupational and experimental studies have shown that the lung, liver, and hematopoietic system are the target organ systems following inhalation exposure to thorium. No relationship was found, however, between the measured body burden of thorium in exposed workers and complete blood count parameters (e.g., hemoglobin, red and white blood cell) (Conibear 1983). Target organs systems have not been identified for oral or dermal exposure to thorium.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Chromosomal aberrations have been reported in the lymphocytes of occupationally exposed workers and in *in vitro* studies. Oliveira et al. (2014) conducted *in vitro* analyses to evaluate whether occupational exposure to the multiple metals in Brazilian monazite sand might result in lymphocyte toxicity (cell viability, cell death, and DNA damage). The metals included thorium, cerium, and lanthanum, either individually or combined, with combinations in ratios typically found in monazite sand. Thorium and cerium individually and thorium+cesium+lanthanum did not cause toxicity in human T-lymphocyte leukemia cells during a 48-hour study. However, concentration-related decreasing cell viability was observed with increasing concentrations of thorium+lanthanum mixtures at concentrations ≥0.29 mM thorium + ≥1.17 mM lanthanum at 24 hours or ≥1.56 mM thorium + ≥0.39 mM lanthanum at 48 hours). At 24 hours, concentration-related increased incidence of necrosis was noted; increasing frequency of apoptotic cells was observed at concentrations up to 1.17 mM thorium + 0.29 mM lanthanum, with a decline in apoptosis at higher concentrations. The thorium+lanthanum mixture did not alter the DNA strand break profile. These results indicate that the thorium+lanthanum mixture was cytotoxic.

Some substances can interact with thorium by reducing deposition or increasing excretion of absorbed thorium. Tetracycline reduced the deposition of thorium in rat bone (Taylor et al. 1971). Studies with a

similar actinide element, plutonium, suggest that a thorium-tetracycline complex may be formed, which is excreted rapidly through the kidneys. Chelating agents such as EDTA and diethylenetriaminepentaacetic acid (DTPA) can remove some thorium from the body. Kumar et al. (2012) demonstrated that rats injected with thorium exhibited significantly increased serum levels of the liver enzymes alanine aminotransferase (ALT), AST, and alkaline phosphatase; however, thorium-treated rats that received DTPA treatment exhibited lower levels of these serum liver enzymes, suggestive of a reduction in the severity of thorium-induced liver effects. DTPA also appeared to mediate the effects of thorium on oxidative stress in the liver.