

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to thorium. Its purpose is to present levels of significant exposure for thorium based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of thorium and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual levels of exposure used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed.

Thorium is a relatively reactive, metallic radioactive element. Because thorium is a radioactive element, evaluation of adverse health effects due to exposure to thorium requires a slightly different approach than with chemicals. Radiation is a health risk because radioactive elements can emit energetic particles or electromagnetic radiation that can damage cells. Radioactive elements are those that undergo spontaneous

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disintegration (decay) in which energy is released (emitted) either in the form of particles, such as alpha or beta particles, or rays, such as gamma or x-rays. This disintegration or decay results in the formation of new elements, some of which may themselves be radioactive, in which case they will also decay. The process continues until a stable (non-radiative) state is reached (see Appendix B for more information). The rate of emission of alpha particles from thorium is low, and the rate of emission of gamma rays is very low (see Chapter 3). Alpha particles are unable to deeply penetrate skin, but can travel short distances in the body (about 4 to 6 cell diameters) if they are emitted from within the body. The intensity and energy of alpha particles emitted depends on the particular isotope of thorium in question. Several isotopes of thorium exist. By mass, the most predominant ones in the environment are thorium-230 (a decay product of uranium-238) and natural thorium (thorium-232) (see Chapter 3). The number of particles emitted is related to the radioactive half-life of the isotope, which is about 14 billion years for natural thorium (thorium-232). The other type of radiation hazard is from gamma rays, which can penetrate the body and pass through the air. However, natural thorium has a very low gamma activity, which means there is little danger from this type of radiation from natural thorium. Daughter products of thorium, however, may emit more gamma radiation than natural thorium (see Chapter 3).

When thorium emits alpha particles, it disintegrates into other daughter radionuclides (radioactive materials), such as radium-226 and radon-222 (from thorium-230 in the uranium-238 decay series) or radium-228 and thoron (radon-220 from thorium-232 in the thorium decay series). It eventually decays to stable lead-208 or -206, which is not radioactive. More information about the decay of thorium can be found in Chapter 3. The toxicological characteristics of radon, radium, and lead are the subject of separate ATSDK Toxicological profiles.

The decay rate or activity of radioactive elements has traditionally been specified in curies (Ci). The curie is approximately 37 billion disintegrations (decay events) per second (3.7×10^{10} dps). In discussing thorium, a smaller unit, 1×10^{-12} Ci, the picocurie (pCi) is used, where pCi is equal to 1 in international usage, the S.I. unit (the International System of Units) for activity is the Becquerel (Bq), which is equal to 1 disintegration per second or about 27 pCi. (Information for conversion between units is given in Appendix B.) Measurements of radioactivity, expressed as nCi (nanocurie), in the environment are more sensitive than units of mass. For this reason, amounts of thorium are expressed in pCi units in Chapter 5. In animal studies, the exposure levels were usually reported in mg (milligrams), but have been converted to activity units (nCi and Bq) for presentation in Chapter 2. The absorbed dose from radiation can be expressed in units of rads or it can be stated in terms of dose equivalent, which includes a modification to reflect the quality of the radiations, for radiation protection purposes, and is expressed in terms of rems. For alpha radiations a quality factor, Q , of 20 is used to convert absorbed dose to dose equivalent.

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Both large and small amounts of radiation are damaging to health. Current scientific consensus is radiation can also increase the probability of cancer, and a conservative assumption is no threshold level exists below which there is no additional risk of cancer. There is considerable debate about how great the cancer risks are when people are chronically exposed to very low levels of radiation. Since everyone is environmentally exposed to a small amount of radiation, the minimum amount of additional radiation that may constitute a health hazard is not well known.

The following sections summarize the health effects associated with thorium. Evidence exists that most, if not all, effects of thorium may be due to its radiological, and not chemical, effects. The mechanism of toxicity for all effects are not well understood. For more information about radiation, see Appendix B.

2.2.1 Inhalation Exposure

2.2.1.1 Death

Two epidemiology studies have examined mortality among thorium workers neither found significant excess mortality. The standard mortality ratio (SMR) for all causes of death in a cohort of 3039 male workers in a thorium processing plant was 1.05 in comparison to United States white males (Polednak et al. 1983). The estimated radiation levels to the workers for inhalation intake ranged from 0.003-0.192 nCi/m³ (0.001-0.007 Bq/m³) for a period of 1-33 years. No evidence of overt industrial disease was found in a cohort of 84 workers at a thorium refinery exposed to <0.045-450 nCi/m³ (<0.002-0.02 Bq/m³) for <1-20 years (Albert et al. 1955). In both studies, the workers were exposed to other toxic compounds (uranium dust) as well as other radioactive materials (thoron, uranium daughters, thorium daughters, cerium).

No compound-related mortality was found in mice exposed to 114-330 Mg/m³ (12.54-36.3 nCi/m³ = 464-1343 Bq/m³) thorium nitrate intermittently for 18 weeks (Patrick and Cross 1948). No compound-related mortality was found in rats, guinea pigs, rabbits, or dogs exposed intermittently for 1 year to 5 mg thorium/m³ (0.550 nCi/m³ = 20 Bq/m³) as thorium dioxide (Hodge et al. 1960). These NOAEL values are reported in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Respiratory Effects. Although the SMR for respiratory diseases was 1.31 among workers at a thorium refinery (Polednak et al. 1983), the increase may have been attributable in part to smoking. Exposure level estimates for inhalation intakes ranged from 0.003-0.192 nCi/m³ (0.001-0.007 Bq/m³) for a period of 1-33 years. Because the workers were exposed to

TABLE 2-1. Levels of Significant Exposure to Thorium - Inhalation

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL ₃ (nCi/m ³)	LOAEL (Effect)		Reference	Chemical Form
					Less Serious (nCi/m ³)	Serious (nCi/m ³)		
INTERMEDIATE EXPOSURE								
Death								
1	Mouse	18 weeks 5 days/week 40 minutes/day		36.3			Patrick and Cross 1948	ThNO ₃
Systemic								
2	Dog	304 days 5 days/week 6 hours/day	Hemato		0.9 ^a (decreased RBC)		Hall et al. 1951	TF ₄
CHRONIC EXPOSURE								
Death								
3	Rat	14 months 5 days/week 6 hours/day		0.55			Hodge et al. 1960	ThO ₂
4	Gn Pig	14 months 5 days/week 6 hours/day		0.55			Hodge et al. 1960	ThO ₂
5	Rabbit	14 months 5 days/week 6 hours/day		0.55			Hodge et al. 1960	ThO ₂
6	Dog	14 months 5 days/week 6 hours/day		0.55			Hodge et al. 1960	ThO ₂
Systemic								
7	Rat	14 months 5 days/week 6 hours/day	Resp Hemato Musc/skel Hepatic Renal	0.55 0.55 0.55 0.55 0.55			Hodge et al. 1960	ThO ₂

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL ^a (nCi/m ³)	LOAEL (Effect)		Reference	Chemical Form
					Less Serious (nCi/m ³)	Serious (nCi/m ³)		
8	Gn Pig	14 months 5 days/week 6 hours/day	Resp	0.55			Hodge et al. 1960	ThO ₂
			Hemato	0.55				
			Musc/skel	0.55				
			Hepatic	0.55				
			Renal	0.55				
9	Rabbit	14 months 5 days/week 6 hours/day	Resp	0.55			Hodge et al. 1960	ThO ₂
			Hemato	0.55				
			Musc/skel	0.55				
			Hepatic	0.55				
			Renal	0.55				
10	Dog	14 months 5 days/week 6 hours/day	Resp	0.55			Hodge et al. 1960	ThO ₂
			Hemato	0.55				
			Musc/skel	0.55				
			Hepatic	0.55				
			Renal	0.55				

^aThe mg/m³ equivalent of 0.9 nCi/m³ is 8.3 mg/m³. This value is converted to an equivalent concentration of 1.8 ppm for presentation in Table 1-2.

Gn Pig = guinea pig; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; RBC = red blood cell; Resp = respiratory; TF₄ = thorium tetrafluoride; ThNO₃ = thorium nitrate; ThO₂ = thorium dioxide.

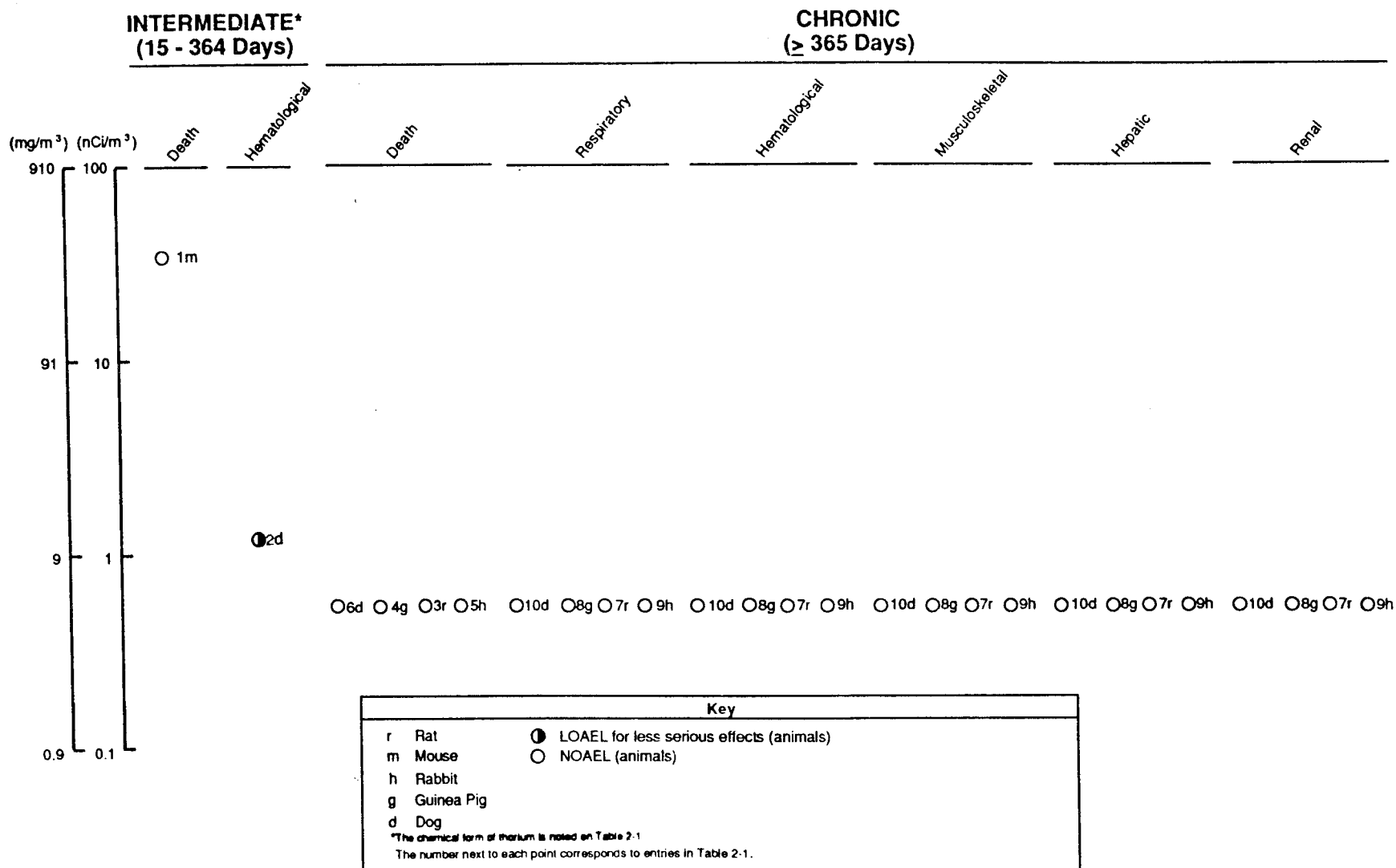


FIGURE 2-1. Levels of Significant Exposure to Thorium - Inhalation

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other toxic compounds (uranium dust) as well as other radioactive metals, toxic effects cannot necessarily be attributed to thorium. Therefore, no quantitative information from the study is reported in Table 2-1 or Figure 2-1.

Progressive cirrhosis of the lungs was found in a subchronic inhalation study in rats (Likhachev et al. 1973a). Rats were exposed intermittently for 6-9 months to an inert aerosol (control), to the inert aerosol enriched with 10% or 49% insoluble thorium dioxide, or to thorium dioxide (100%) alone. The severity of the lung cirrhosis was directly related to the radiation dose and the amount of thorium dioxide. Cirrhosis of the lungs became evident in 3-6 months in the 100% thorium dioxide group, in 9-12 months in the 49% thorium dioxide group, in 12-15 months in the 10% thorium dioxide group, and in 18-24 months in the inert aerosol control group. At lung exposures of up to 150 rad, reticulosarcoma was found, while at lung exposures of 100-2700 rad, glandular cancerous tumors were found (see Section 2.2.1.8). The tumors may have been caused by thorium dioxide; the exact amount of thorium administered was not clear from the report, so the results of the study do not appear in Table 2-1 or Figure 2-1.

No histopathological effects on the lungs were found in rats, guinea pigs, rabbits, or dogs exposed intermittently for 1 year to 5 mg thorium/m³ (0.550 nCi/m³ = Bq/m³) as thorium dioxide (Hodge et al. 1960). This NOAEL value is presented in Table 2-1 and plotted in Figure 2-1.

Hematological Effects. A complete blood count (CBC) was done on a cohort of 273 male monazite sand refinery workers to determine the effect of thorium on the hematological system. The measured body burden (calculated from in vivo detection of external gamma rays emitted by daughter products of thorium still in the subject's body and from thoron in expired air) of thorium was higher in those workers exposed for a longer time period, but the blood count did not correlate with the body burden of thorium (Conibear 1983). A correlation was found, however, between the blood count and cigarette smoking habits. Exposure level estimates for inhalation intakes of nicotine or thorium were not reported, and the external gamma-ray exposure rate was between 0.5 and 5.0 mR/hour. Because the workers were exposed to other toxic compounds (silica, yttrium, acid and alkali fumes) as well as other sources of radioactivity, toxic effects cannot necessarily be attributed to thorium. Therefore, the results of the study do not appear in Table 2-1 or Figure 2-1.

Effects on hematological parameters (abnormal forms of monocytes, lymphocytes and granulocytes, hypoplastic bone marrow, red cell count depression, macrocytosis, increase in immature granulocytes) were found in dogs exposed 6 hours/day, 5 days/week to various chemical forms of thorium: thorium nitrate tetrahydrate for 60 days (4 nCi/m³ = 150 Bq/m³); thorium dioxide for 60 days (4.8 nCi/m³ = 180 Bq/m³); thorium tetrafluoride for 304 days (0.9 nCi/m³ = 33 Bq/m³); thorium oxalate for 270 days (1.4 nCi/m³ = 52 Bq/m³) (Hall et al. 1951). Differences in the degree of toxicity of the

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various chemical forms of thorium on hematological parameters could not be determined from this study, although gagging, retching, and occasional vomiting were found periodically in the dogs exposed to thorium nitrate tetrahydrate. The lowest LOAEL, thorium tetrafluoride ($0.9 \text{ nCi/m}^3 = 33 \text{ Bq/m}^3$), is reported on Table 2-1 and plotted on Figure 2-1.

No effects on hematological parameters, blood nonprotein nitrogen (NPN), or the histopathology of the spleen were found in rats, guinea pigs, rabbits, or dogs exposed for 1 year to 5 mg/thorium m^3 ($0.550 \text{ nCi/m}^3 = 20 \text{ Bq/m}^3$) as thorium dioxide (Hodge et al. 1960). This NOAEL value is presented in Table 2-1 and plotted in Figure 2-1.

Musculoskeletal Effects. No studies were located regarding the musculoskeletal effects in humans after inhalation exposure to thorium.

Upon histopathological examination, no effects in the femur were found. In rats, guinea pigs, rabbits, or dogs exposed for 1 year to 5 mg thorium/m^3 ($0.550 \text{ nCi/m}^3 = \text{Bq/m}^3$) as thorium dioxide (Hodge et al. 1960). This NOAEL value is presented in Table 2-1 and plotted in Figure 2-1.

Hepatic Effects. The levels of aspartate aminotransferase, globulin, and total bilirubin in sera of a cohort of 275 former workers in a thorium refinery were correlated with body burdens of radioactivity (Farid and Conibear 1983). The levels of aspartate aminotransferase and total bilirubin were significantly higher ($p < 0.0001$ and $p = 0.043$, respectively) in thorium-exposed workers, as compared to U.S. white males. Globulin levels also increased with increasing levels of body burden, but not significantly. Although the enzymatic levels tested were elevated, they were still within the normal range. No effects on albumin, total protein, or alkaline phosphatase were seen. The correlation of hepatic function tests with body burden of radioactivity may suggest a radiotoxic effect, but this was not proven by the authors. No exposure concentrations were reported.

No histopathological effects in the liver were found in rats, guinea pigs, rabbits, or dogs exposed to 5 mg thorium/m^3 ($0.550 \text{ nCi/m}^3 = 20 \text{ Bq/m}^3$) for 1 year as thorium dioxide (Hodge et al. 1960). This NOAEL value is presented in Table 2-1 and plotted in Figure 2-1.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to thorium.

No histopathological effects in the kidneys were found in rats, guinea pigs, rabbits, or dogs exposed to 5 mg thorium/m^3 ($0.550 \text{ nCi/m}^3 = 20 \text{ Bq/m}^3$) for 1 year as thorium dioxide (Hodge et al. 1960). This NOAEL value is presented in Table 2-1 and plotted in Figure 2-1.

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2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans after inhalation exposure to thorium. No histopathological effects in the lymph nodes were found in rats, guinea pigs, rabbits, or dogs exposed to 5 mg thorium/m³ (0,550 nCi/m³ = 20 Bq/m³) for 1 year as thorium dioxide (Hodge et al. 1960). Since no parameters of immune function were examined, this value does not appear as a NOAEL for immunological effects in Table 2-1 or Figure 2-1.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to thorium.

2.2.1.4 Neurological Effects

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

Hoegerman and Cummins (1983) assessed the frequency of chromosome aberrations in the lymphocytes of 47 male workers in a thorium processing plant. The workers were divided into three groups based on their body burdens of radioactivity: low (0 nCi/kg), moderate (0.003 nCi/kg = 0.11 Bq/kg) and high (0.015 nCi/kg = 0.56 Bq/kg) body burden groups. An increased frequency of chromosomal aberrations (dicentric ring chromosomes) were found in the high burden groups (combined high and moderate burden groups) compared to the low burden group and historical controls. No significant differences were found in the frequency of two-break chromosome aberrations. A positive correlation was not established between the frequency of chromosomal aberrations and duration of employment. The observed aberration frequency was generally compatible with that found in patients injected with thorium dioxide colloid (Thorotrast) (see Section 2.2.4.7). Costa-Ribeiro et al. (1975) also reported a statistically significant ($p < 0.05$) increase in the number of chromosomal aberrations (dicentrics) in 240 monazite sand millers, as compared to controls. No significant differences in the incidence of translocations were observed. No exposure concentrations were reported in either study.

No studies were located regarding genotoxic effects in animals after inhalation exposure to thorium.

2.2.1.8 Cancer

A statistically significant excess of deaths from pancreatic cancer was seen in a cohort of 3039 former thorium workers employed for 1 year or more (6 observed vs. 1.3 expected) but not in workers employed for a shorter time

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(3 observed vs. 2.7 expected) (Stehney et al. 1980). The workers were exposed to 0.003-0.192 nCi/m³ (0.001-0.007 Bq/m³). Although a correlation between smoking and pancreatic cancer has not been established, the excess mortality may be due, in part, to the fact that a higher proportion of smokers was found in the worker population when compared to U.S. white males (ratio of 1.3 observed smokers/expected smokers). A second study compared the SMR of workers in a thorium processing plant to the mortality rates for U.S. white males and determined that the SMRs in the workers were high for deaths due to lung cancer (SMR=1.44; 95% confidence limit 0.98 and 2.02) and pancreatic cancer (SMR=2.01; 95% confidence limit 0.92 and 3.82) (Polednak et al. 1983). In a subgroup of men in jobs with the highest exposure to thorium, the SMR for lung cancer was 1.68 and the SMR for pancreatic cancer was 4.13. Exposure level estimates for inhalation intakes ranged from 0.003-0.192 nCi/m³ (0.0001-0.007 Bq/m³) for a period of 1-33 years. The authors indicated that smoking may be a confounding factor in the increased rates of cancer and that the workers were exposed to other potentially carcinogenic agents, such as thoron (radon-220). Consequently, the evidence for a causal relationship between thorium exposure and cancer is not convincing and no concentrations are reported in Table 2-1 or plotted in Figure 2-1.

A significantly ($p < 0.05$) increased incidence of malignancies in the lymphatic and hematopoietic tissues of uranium mill workers (cohort of 662 males) was found by Archer et al. (1973). The radioactivity in the tracheobronchial lymph nodes of the workers was found to be primarily the result of alpha emissions from thorium-230 and not from uranium-234 or uranium-238. Consequently, the authors suggested that the increased incidence of malignancies may have been a result of thorium-230 exposure and not uranium exposure. Exposure levels of thorium were not reported; therefore, the results of the study are not reported on Table 2-1 or plotted in Figure 2-1.

Rats were exposed to various concentrations of thorium dioxide for 6-9 months, and the frequency and histological type of lung tumors were determined following observation for up to 21 months (Likhachev et al. 1973b; Likhachev 1976). The authors concluded that the incidence and histological type of lung tumors that developed were dependent on the radiation dose to the lungs. At lung doses of up to 150 rad (3000 rems), primarily reticulosarcoma was found (in 16% of the animals), while at total doses of 1000-2700 rads (20,000-54,000 rems), glandular cancerous tumors (adenomatosis and squamous cell carcinoma) were found in all of the exposed animals, and the reticulosarcoma was no longer observed.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding lethal effects in humans after oral exposure to thorium.

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A single gavage administration of 1000 mg thorium/kg body weight/day (110 nCi/kg/day = 4070 Bq/kg/day) as thorium nitrate resulted in the death of 4/20 mice, while a single amount of 760 mg thorium/kg body weight/day (84 nCi/kg/day = 3100 Bq/kg/day) resulted in no mortality. Occasional intestinal hemorrhage was noted at autopsy in the mice that died, but it was not reported if the hemorrhage was the cause of death in the animals. No effects were found following administration of a 10% sodium nitrate solution, suggesting that the adverse effects were due to thorium and not to nitrate (Patrick and Cross 1948). Following 4 months of continuous exposure to 123 mg thorium/kg body weight/day (13.6 nCi/kg/day = 503 Bq/kg/day) as thorium nitrate in the drinking water, 50% of the treated mice and 10% of the control mice died (Patrick and Cross 1948). No cause of death was reported in either the acute or the 4-month studies. In rats, 4 months of exposure to 3043 mg thorium/kg body weight/day (335 nCi/kg/day = 12,400 Bq/kg/day) as thorium nitrate resulted in death, but the deaths may have been due to the poor nutritional state of the animals since the treated animals ate much less of the treated food and, therefore, lost weight (Downs et al. 1959).

Death occurred following four daily administrations of ≥ 2130 mg thorium/kg body weight/day (234 nCi/kg/day = 8657 Bq/kg/day) as thorium nitrate in the food to a single dog (Patrick and Cross 1948). No immediate deaths were reported following a single administration of 121 mg thorium/kg body weight/day (13 nCi/kg/day = 481 Bq/kg/day) by gavage as thorium nitrate to dogs (Sollman and Brown 1907). Death was not found following exposure of a single dog to food containing 426 mg thorium/kg body weight/day (47 nCi/kg/day = 1740 Bq/kg/day) as thorium nitrate for 46 days (Downs et al. 1959). No deaths were reported following a single gavage administration of thorium nitrate (483 mg thorium/kg body weight/day = 53 nCi/kg/day = 1960 Bq/kg/day) in rabbits (Sollman and Brown 1907). The number of treated and control animals (dogs and rabbits) was not reported in the Sollman and Brown (1907) study.

All reliable NOAEL and LOAEL values are reported in Table 2-2 and plotted in Figure 2-2. Values from the Sollman and Brown (1907) study are not reported in the table and figure since the number of animals in the study were not reported. The LOAEL value for death in rats from the Downs et al. (1959) study is not reported since the deaths may have been due to the poor nutritional state of the animals and not to thorium toxicity, and the NOAEL and LOAEL values for the death of dogs in the Downs et al. (1959) and the Patrick and Cross (1948) studies, respectively, are not reported since they were pilot studies and only one animal was used.

2.2.2.2 Systemic Effects

Respiratory Effects. No studies were located regarding the respiratory effects in humans after oral exposure to thorium.

TABLE 2-2. Levels of Significant Exposure to Thorium - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (nCi/kg/day)	LOAEL (Effect)		Reference	Chemical Form
						Less Serious (nCi/kg/day)	Serious (nCi/kg/day)		
ACUTE EXPOSURE									
Death									
1	Mouse	(G)	1 day		84		110 ^a (4/20)	Patrick and Cross 1948	ThNO ₃
INTERMEDIATE EXPOSURE									
Death									
2	Mouse	(W)	4 months 7 days/week 24 hours/day				12 ^b (10/20)	Patrick and Cross 1948	ThNO ₃
Systemic									
3	Rat	(F)	4 months 7 days/week 24 hours/day	Resp Cardio Gastro Hemato Hepatic Renal	335 335 335 335 335 335			Downs et al. 1959	ThNO ₃
Reproductive									
4	Rat	(F)	4 months 7 days/week 24 hour/day		335			Downs et al. 1959	ThNO ₃

^aThe mg/kg equivalent of 110 nCi/kg = 1000 mg/kg. This value is converted to an equivalent concentration of ppm in water for presentation in Table 1-4.

^bThe concentration in drinking water was 0.1%. This equals 1000 mg/L = 1000 ppm. This concentration is presented in Table 1-4.

(G) = gavage; Cardio = cardiovascular; (F) = food; Gastro = gastrointestinal; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; ThNO₃ = thorium nitrate; (W) = water.

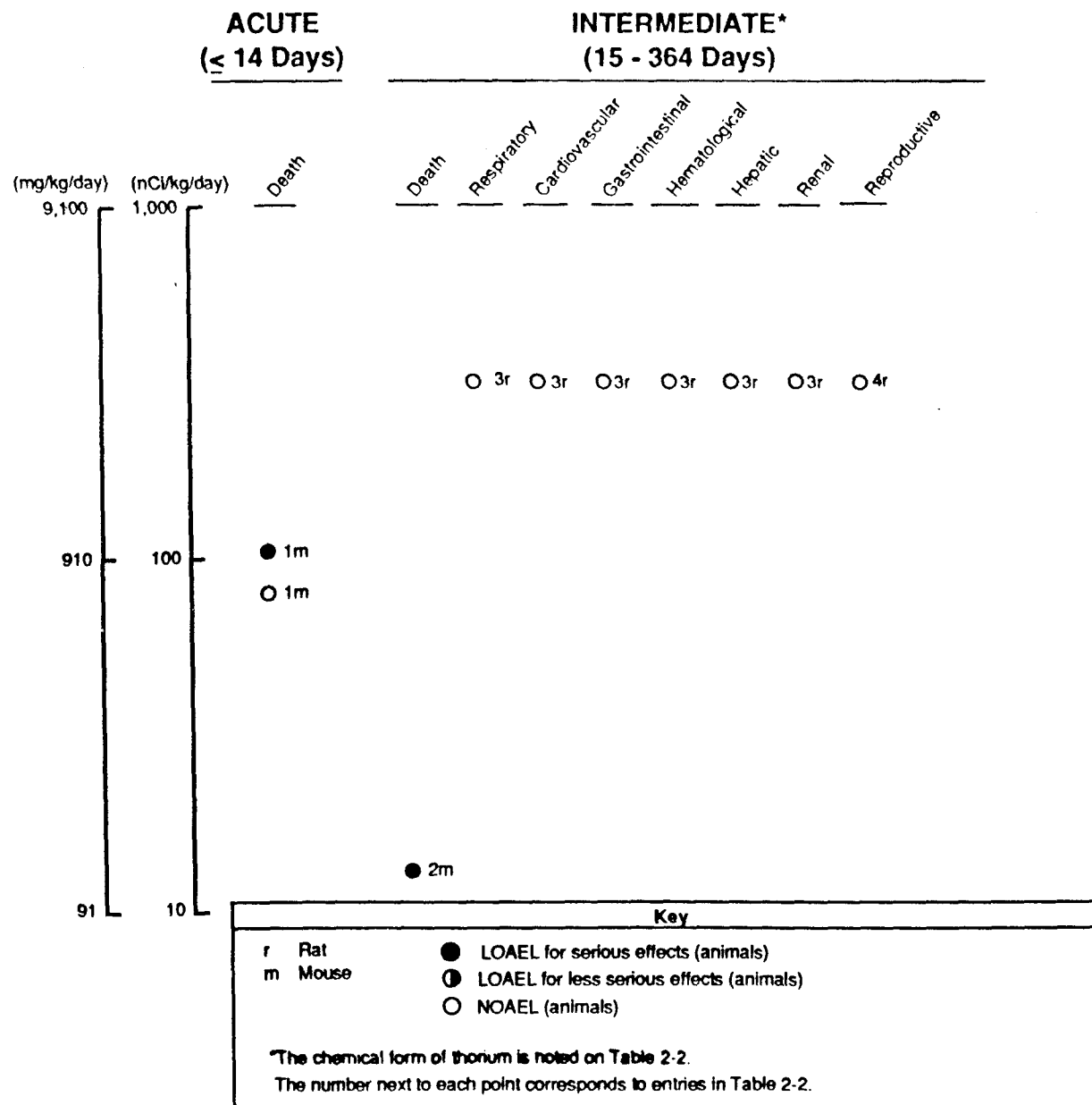


FIGURE 2-2. Levels of Significant Exposure to Thorium - Oral

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No histopathological changes in the lungs were found in rats treated for 4 months with 3043 mg thorium/kg body weight/day (335 nCi/kg/day = 12,400 Bq/kg/day) or in one dog treated for 46 days with 426 mg thorium/kg body weight/day (47 nCi/kg/day = 1740 Bq/kg/day) as thorium nitrate in the food (Downs et al. 1959). These NOAEL values for rats are reported in Tab 2-2 and plotted in Figure 2-2. The NOAEL value for the effects in dogs is not reported since this was a pilot study and only one animal was used.

Cardiovascular Effects. No studies were located regarding the cardiovascular effects in humans after oral exposure to thorium.

No histopathological changes in the heart were found in rats treated for 4 months with 3043 mg thorium/kg body weight/day (335 nCi/kg/day = 12,400 Bq/kg/day) or in one dog treated for 46 days with 426 mg thorium/kg body weight/day (47 nCi/kg/day = 1740 Bq/kg/day) as thorium nitrate in the food (Downs et al. 1959). These NOAEL values for rats are reported in Tab 2-2 and plotted in Figure 2-2. The NOAEL value for the effects in dogs is not reported since this was a pilot study and only one animal was used.

Gastrointestinal Effects. No studies were located regarding the gastrointestinal effects in humans after oral exposure to thorium.

No histopathological changes in the stomach and intestines were found in rats treated for 4 months with 3043 mg thorium/kg body weight/day (335 nCi/kg/day = 12,400 Bq/kg/day) or in one dog treated for 46 days with 426 mg thorium/kg body weight/day (47 nCi/kg/day = 1740 Bq/kg/day) as thorium nitrate in the food (Downs et al. 1959). These NOAEL values for rats are reported in Table 2-2 and plotted in Figure 2-2. The NOAEL value for the effects in dogs is not reported since this was a pilot study and only one animal was used.

Occasional intestinal hemorrhages were reported in mice that died following a single gavage exposure to thorium nitrate (Patrick and Cross 1948). It was not reported whether the intestinal hemorrhage was the cause of death in the mice. The level at which this occurred was not reported. The possibility that intestinal damage resulted from improper gavage technique cannot be ruled out; therefore, these data are not presented in Table 2-2 or plotted in Figure 2-2.

Hematological Effects. No studies were located regarding the hematological effects in humans after oral exposure to thorium.

No histopathological changes in the spleen were found in rats treated for 4 months with 3043 mg thorium/kg body weight/day (335 nCi/kg/day = 12,400 Bq/kg/day) or in one dog treated for 46 days with 426 mg thorium/kg body weight/day (47 nCi/kg/day = 1740 Bq/kg/day) as thorium nitrate in the food (Downs et al. 1959). These NOAEL values for rats are reported in Table 2-2 and plotted in Figure 2-2. The NOAEL value for the effects in

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dogs is not reported since this was a pilot study and only one animal was used.

Hepatic Effects. No studies were located regarding the hepatic effects in humans after oral exposure to thorium.

No histopathological changes in the liver were found in rats treated for 4 months with 3043 mg thorium/kg body weight/day (335 nCi/kg/day = 12,400 Bq/kg/day) or in one dog treated for 46 days with 426 mg thorium/kg body weight/day (47 nCi/kg/day = 1740 Bq/kg/day) as thorium nitrate in the food (Downs et al. 1959). These NOAEL values for rats are reported in Table 2-2 and plotted in Figure 2-2. The NOAEL value for the effects in dogs is not reported since this was a pilot study and only one animal was used.

Renal Effects. No studies were located regarding the renal effects in humans after oral exposure to thorium.

No histopathological changes in the kidneys were found in rats treated for 4 months with 3043 mg thorium/kg body weight/day (335 nCi/kg/day = 12,400 Bq/kg/day) or in one dog treated for 46 days with 426 mg thorium/kg body weight/day (47 nCi/kg/day = 1740 Bq/kg/day) as thorium nitrate in the food (Downs et al. 1959). These NOAEL values for rats are reported in Table 2-2 and plotted in Figure 2-2. The NOAEL value for the effects in dogs is not reported since this was a pilot study and only one animal was used.

Other Systemic Effects. Weight loss was found in rats treated for 4 months with 3043 mg thorium/kg body weight/day (335 nCi/kg/day = 12,400 Bq/kg/day) and in one dog treated for 46 days with 426 mg thorium/kg body weight/day (47 nCi/kg/day = 1740 Bq/kg/day) as thorium nitrate in the food (Downs et al. 1959). The weight loss was attributed to a decrease in intake of the treated food; therefore, these values are not reported in Table 2-2 or Figure 2-2.

No studies were located regarding the following health effects in humans or animals after oral exposure to thorium.

2.2.2.3 Immunological Effects

2.2.2.4 Neurological Effects

2.2.2.5 Developmental Effects

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to thorium.

No histopathological changes in the gonads (exact tissues examined were not reported) were found in male and female rats treated for 4 months with

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3043 mg thorium/kg body weight/day (335 nCi/kg/day = 12,400 Bq/kg/day). No histopathological changes in the testes were found in one dog treated for 46 days with 426 mg thorium/kg body weight/day (47 nCi/kg/day - 1740 Bq/kg/day) as thorium nitrate in the food (Downs et al. 1959). The value of 335 nCi/kg/day for rats is reported in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to thorium.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after oral exposure to thorium.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding lethal effects in humans after dermal exposure to thorium.

Tandon et al. (1975) reported no lethality in rats following dermal application of 529 mg thorium/kg body weight (58 nCi/kg = 2146 Bq/kg), daily for 15 days, to the lateroabdominal and scrotal skin. Prior to treatment, the hair was clipped. The area remained uncovered for the duration of treatment. The thorium was administered as thorium nitrate. This NOAEL value is reported in Table 2-3.

2.2.3.2 Systemic Effects

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to thorium.

Tandon et al. (1975) reported no histopathological effects on the liver of rats following dermal application of 529 mg thorium/kg body weight/day (58 nCi/kg/day - 2146 Bq/kg/day) for 15 days to the lateroabdominal and scrotal areas. Prior to treatment, the hair was clipped. The area remained uncovered for the duration of treatment. The thorium was administered as thorium nitrate. This NOAEL value for hepatic effects in rats is reported in Table 2-3.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to thorium.

TABLE 2-3. Levels of Significant Exposure to Thorium - Dermal

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (nCi/kg)	LOAEL (Effect)		Reference	Chemical Form
					Less Serious (nCi/kg)	Serious (nCi/kg)		
INTERMEDIATE EXPOSURE								
Death								
1	Rat	15 days		58			Tandon et al. 1975	ThNO ₃
Systemic								
2	Rat	15 days	Hepatic Renal Derm	58 58	15 (hyperkeratin)	58 (acanthosis)	Tandon et al. 1975	ThNO ₃
Reproductive								
3	Rat	15 days			15 (tubule edema)	58 (abnormal sperm)	Tandon et al. 1975	ThNO ₃

Derm = dermal; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; ThNO₃ = thorium nitrate.

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Tandon et al. (1975) reported no histopathological effects on the kidneys of rats following dermal application of 529 mg thorium/kg body weight/day (58 nCi/kg/day = 2146 Bq/kg/day) for 15 days to the lateroabdominal and scrotal areas. Prior to treatment, the hair was clipped. The area remained uncovered for the duration of treatment. The thorium was administered as thorium nitrate. This NOAEL value for renal effects in rats is reported in Table 2-3.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after dermal exposure to thorium.

Tandon et al. (1975) applied daily dermal applications of 132.5 mg thorium/kg body weight/day (15 nCi/kg/day = 555 Bq/kg/day), 265 mg thorium/kg body weight/day (29 nCi/kg/day = 1073 Bq/kg/day), or 529 mg thorium/kg body weight/day (58 nCi/kg/day = 2146 Bq/kg/day) to the lateroabdominal and scrotal areas of rats for 15 days. The thorium was administered to skin (hair was clipped) as thorium nitrate, and the area remained uncovered for the duration of treatment. Mild hyperkeratinization of the lateroabdominal skin was found at all exposure levels. At the highest exposure level, mild acanthosis and thickening of the epithelial lining of the lateroabdominal skin were seen. At this level, mild acanthosis, swollen collagen fibers, and foamy dermis were found in the scrotal skin. The value of 15 nCi/kg/day is a less serious LOAEL, and the exposure level of 58 nCi/kg/day is a serious LOAEL for dermal effects in the rat. These values are reported in Table 2-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to thorium.

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to thorium.

Tandon et al. (1975) applied daily dermal applications of 132.5 mg thorium/kg body weight/day (15 nCi/kg/day = 555 Bq/kg/day), 265 mg thorium/kg body weight/day (29 nCi/kg/day = 1073 Bq/kg/day), or 529 mg thorium/kg body weight/day (58 nCi/kg/day = 2146 Bq/kg/day) to the lateroabdominal and scrotal skin of rats for 15 days. The thorium was administered to skin (hair was clipped) as thorium nitrate, and the area remained uncovered for the duration of treatment. Mild edema of the seminiferous tubules and the interstitium was seen at all exposure levels. At the highest exposure level, some desquamation of sperm and giant

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spermatid-type cells were found. The percentage of sperm affected by thorium treatment was not reported. It was not clear whether these reproductive changes were due to chemical or radiation effects, although they were more likely the result of chemical toxicity because of the short time required to produce the effects. The level of 15 nCi/kg/day is a less serious LOAEL and 58 nCi/kg/day is a serious LOAEL for the reproductive effects of thorium in rats. These values are reported in Table 2-3.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to thorium.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to thorium.

2.2.4 Other Routes of Exposure

Most of, the literature deals with the carcinogenic effects of thorium as a result of intravenous injection of Thorotrast, a colloid consisting of approximately 25% thorium-232 dioxide and stabilized with dextran. Thorotrast was used as a radiographic contrast medium between the years 1928 and 1955. It was estimated that 50,000-100,000 patients worldwide received Thorotrast (Harrist et al. 1979; Isner et al. 1978). Generally, 10-75 mL of Thorotrast was injected and toxic effects were found at all exposure -levels. It has been reported that the thorium-232 in Thorotrast has an activity of 24.2 nCi/mL (Steinstrasser 1981); therefore, the injected amounts of 1-75 mL correspond to 3.5-26 nCi/kg body weight (129-962 Bq/kg). The toxic effects include formation 4-6 years after exposure of "Thorotrastomas," granulomas at the site of injection resulting from the extravasation of the injected Thorotrast (Frank 1980; Grampa 1971). Blood disorders (hemolytic and aplastic anemia, myelofibrosis, and leukemia) appeared 20 years following injection, and hemangiosarcoma of the liver was found 25-30 years post-exposure (Frank 1980). A relationship was found between the amount of the Thorotrast injected and the incidence of liver tumors (cholangiocarcinoma, angiosarcoma, hepatic cellular carcinoma) (Wesch et al. 1983; Van Kaick et al. 1983). A decrease in the time to tumors was also found with increased injected volume of Thorotrast (Van Kaick et al. 1983). The use of Thorotrast ceased when the potential toxic effects were recognized.

2.2.4.1 Death

No studies were located regarding acute lethal effects in humans after other routes of exposure to thorium. Death from various types of cancer, however, was found 20-30 years after intravenous injection of Thorotrast.

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After a period of 15 months, no increased mortality was seen from a single intravenous injection of 0.5 mL of Thorotrast (403 nCi/kg = 14909 Bq/kg) in mice (Guimaraes et al. 1955).

2.2.4.2 Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans after other routes of exposure to thorium. No degenerative changes in the pulmonary parenchyma were found, but 7/20 mice that died 15 months after intravenous injection of Thorotrast (Guimaraes et al. 1955) and 8/20 mice that were sacrificed 5-12 months after injection of Thorotrast (Guimaraes and Lamerton 1956) had lung adenomas. There was no significant difference in survival between the treated and control animals in either study. In a few cases, an association between the presence of Thorotrast deposits in the lungs and the proliferation of bronchioles and alveoli was found.

Cardiovascular Effects. Myocardial infarction, severe coronary luminal narrowing, and internal alteration of the carotid artery were found in two patients injected 21-30 years before with an unreported amount of Thorotrast (Isner et al. 1978). The authors concluded that the vascular effects were the result of chronic alpha irradiation. The patients were injected in the carotid artery, and thorotrastoma (see Other Systemic Effects, below) was found in both patients.

Lipchik et al. (1972) reported no significant acute changes in cardiac output, pulse rate, pressure or left ventricle volumes, or clotting time in dogs injected intravenously with up to 1 mL of Thorotrast/kg (1.9 nCi/kg = 70 Bq/kg).

Eleven months after intratracheal and intraperitoneal injection of thorium dioxide in rats, a sharp and persistent fall in blood pressure was found (Syao-Shan 1970). The fall in blood pressure could not be directly attributed to the chemical or radiological effects of thorium.

Hematological Effects. Aplastic anemia, leukemia (erythroleukemia, acute myelogenous leukemia), myelofibrosis, and splenic cirrhosis were among the hematological effects commonly found in patients after injection of Thorotrast (Dejgaard et al. 1984; Kamiyama et al. 1988; Kato et al. 1983; Rao et al. 1986; Summers and Chung 1986; Van Kaick et al. 1983). The appearance of the leukemia commonly occurred 20 years after injection (see Section 2.2.4.8).

No studies were located regarding hematological effects in animals after other routes of exposure to thorium.

Hepatic Effects. Severe cirrhosis of the liver was one of the primary systemic effects seen following injection of Thorotrast in humans (Baxter

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et al. 1980a,b; Faber 1979; Kato and Kido 1987; Kato et al. 1983; Mori et al. 1979, 1983a,b; Rao et al. 1986; Van Kaick et al. 1983). Cases of fibrosis, veno-occlusive disease, and blood-filled cavities were also found in the livers of Thorotrast patients (da Silva Horta 1967a; Dejgaard et al. 1984). The latency period for the appearance of the cirrhosis was not clear, but was probably comparable to the latency period for liver tumors (25-30 years) since the two effects were often found together.

Degenerative liver changes (necrosis, fibrosis, cirrhosis) were found in mice and rats treated with a single dose of Thorotrast and allowed to survive up to 15 months after treatment (Guimaraes et al. 1955; Guimaraes and Lamerton 1956; Wegener et al. 1983). The authors of the mouse study (Guimaraes et al. 1955; Guimaraes and Lamerton, 1956) concluded that radiation was responsible for the cellular proliferation that led to the degeneration and hepatic tumors.

Following intravenous injection of 0-2.8 $\mu\text{Ci/kg}$ (104,000 Bq/kg) thorium-227 in a solution of citric acid-sodium citrate buffer in dogs, an increase in serum alkaline phosphatase measurements and hypoalbuminemia and hyperglobulinemia were observed (Stevens et al. 1967). No effects on the levels of serum glutamic pyruvic transaminase (SGPT) or serum glutamic oxaloacetic transaminase (SGOT) were found.

Renal Effects. No studies were located regarding renal effects in humans or animals after other routes of exposure to thorium, but tumors of the kidney have been reported after intravenous administration of thorium in humans (see Section 2.2.4.8).

Other Systemic Effects. Localized fibrosis infiltrated with macrophages was often found surrounding deposits of Thorotrast at the point of intravenous injection. These granulomas were termed Thorotrastoma and resulted from fibroblastic proliferation due to the extravascular deposition of Thorotrast (Coorey 1983; Stanley and Calcaterra 1981; Stougaard et al. 1984; Wustrow et al. 1988). Histologically, the Thorotrastoma consisted of dense, hyalinized connective tissue with Thorotrast found both free and in the cytoplasm of macrophages (Grampa 1971). The Thorotrastoma most commonly occurred in the neck after a cerebral angiography and appeared 4-6 years after intravenous injection (Frank 1980).

2.2.4.3 Immunological Effects

Fibrosis of the lymph nodes, which occluded the lymph vessels, and of the spleen were found in patients injected intravenously with unknown quantities of Thorotrast (da Silva Horta 1967a; Wegener et al. 1976; Wegener and Wesch 1979). No malignancies were found in the lymph nodes, but hemangioendothelioma of the spleen was reported in 2/14 patients examined by da Silva Horta (1967a).

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No degenerative changes were observed in the spleen of mice injected intravenously with Thorotrast, but one animal had a malignant hemangioendothelioma (Guimaraes et al. 1955). Michael and Murray (1970) found a suppression in immune response following administration of Thorotrast to mice. The suppression was found to appear sooner (within 1 hour after treatment) and last for a longer period of time (up to 3 days) when Thorotrast was administered intraperitoneally rather than intravenously. Thorotrast was found to affect lymphoid cells involved in antibody formation, as well as the blockade of phagocytic cells in certain organs of the reticuloendothelial system (Michael and Murray 1970).

No studies were located regarding the following health effects in humans or animals after other routes of exposure to thorium:

2.2.4.4 Neurological Effects

2.2.4.5 Developmental Effects

2.2.4.6 Reproductive Effects

2.2.4.7 Genotoxic Effects

The intravenous injection of Thorotrast resulted in radiation-induced chromosomal aberrations in patients (Fischer et al. 1967; Kemmer 1979; Kemmer et al. 1971, 1979; Sadamori et al. 1987; Sasaki et al. 1987). A positive correlation was found between the chromosomal aberration rate and the administered amount of Thorotrast (Buckton and Langlands 1973; Fischer et al. 1967; Kemmer et al. 1971, 1973).

No studies were located regarding the genotoxic effects in animals after intravenous injection or other routes of exposure to thorium.

2.2.4.8 Cancer

The primary effects of intravenously injected Thorotrast in humans are liver tumors (cholangiocarcinoma, angiosarcoma, hepatic cellular carcinoma) and blood disorders (aplastic anemia, erythroleukemia, acute myelogenous leukemia) (BEIR IV 1988; Ito et al. 1988; Kamiyama et al. 1988; Kato and Kido 1987; Kojirs et al. 1985; Levy et al. 1986; Van Kaick et al. 1983; Yamada et al. 1983). Two groups of former Thorotrast patients were examined (one group was 93 autopsy cases from the "Annual of Pathological Autopsy Cases" in Japan and the other was a group of 78 autopsy cases from the Japanese literature). Cholangiocarcinoma was found in 55-58%, angiosarcoma was found in 24-25%, and hepatocellular carcinoma was found in 17-21% of these cases (Yamada et al. 1983). The mean latency period for all tumor types was between 25 and 30 years (Frank 1980). The mean value of absorbed dose to the liver was calculated to be 876 rads for hepatocellular carcinoma and 1053 rads for cholangiocarcinoma (Mori et al. 1983b). It was determined that angiosarcoma developed later (33.5-year mean latency period) than

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cholangiocarcinoma (27.8 years) (Yamada et al., 1983). Blood-filled cavities in the tumors were common (Visfeldt and Poulsen 1972). Kato et al. (1983) reported that malignant hepatic tumors accounted for 63% of all Thorotrast-related deaths, and as the dose rate increased (<15 to ≥ 45 rad/year; <0.15 to ≥ 0.45 Gy/year), the severity of the liver effects increased and the latency period decreased. A dose-effect relationship was found between the amount of Thorotrast injected and the incidence of liver tumors in humans (Van Kaick et al. 1983). The radiation dose to the liver from 1-10 mL injected was 10 rad/year (0.10 Gy/year), 11-20 mL was 18 rad/year (0.18 Gy/year), and >20 mL was 30 rad/year (0.30 Gy/year).

The latency period for leukemia was about 20 years, which was 5-10 years shorter than the liver tumors (Frank 1980). The primary forms of leukemia found were erythroleukemia and acute myelogenous leukemia (da Motta et al. 1979; Kamiyama et al. 1988; Mori et al. 1983b). Kamiyama et al. (1988) reported that the damage from Thorotrast may have been due to effects on the hematopoietic stem cell level.

Fifteen cases of bone tumors resulting from intravenous Thorotrast injection have been reported (9 of which were osteosarcoma). The mean latency period was 26 years and the latency period and injected amount of Thorotrast were inversely related (Harrist et al. 1979). The mean dose rate to bone was 16 rads/year (0.16 Gy/year) per 25 mL of injected Thorotrast (Van Kaick et al. 1983).

Tumors of the kidneys, spleen, and pancreas have also been reported (Christensen et al. 1983; Guimaraes et al. 1955; Kauzlaric et al. 1987; Levy et al. 1986; Mori et al. 1979; Van Kaick et al. 1983; Westin et al. 1973). Christensen et al. (1983) determined that transitional cell carcinoma of the kidneys have a significantly longer latency period (35.8 years; $p < 0.005$) compared to carcinoma of other histological types (27.6 years). A few cases of meningioma and gliosarcoma were found (da Silva Horta 1967b; Kyle et al. 1963; Sussman et al. 1980; Wargotz et al. 1988).

The literature suggests that the toxic effects of Thorotrast are due to the alpha radiation effects of thorium and not to the chemical effects of thorium or of the colloid (Faber 1973; BEIR IV 1988; Taylor et al. 1986; Wesch et al. 1983). Wesch et al. (1983) injected Thorotrast enriched with thorium-230 into rats and found a linear relationship between radiation level and tumor incidence. At a constant radioactive level, an increase in the injected colloidal volume had little influence on the number of liver tumors, but resulted in a decrease in tumor appearance time and, therefore, a decrease in lifespan. The larger colloidal volume may result in a more diffuse organ dose and a less "hot spot" distribution. Injection of the nonradioactive colloid resulted in no appreciable incidence of liver tumors. It is not known whether the colloidal particles induce the liver tumors when given in combination with the radioactive thorium, or if the colloid only accelerates the expression of the radiation-induced tumors. However,

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studies in mice reported by Taylor et al. (1986) suggest that the induction of liver cancer can be accounted for by the radiation alone.

Thorotrast studies in rats found a positive correlation between the administered amount and the number of liver and splenic tumors (Johansen 1967; Wesch et al. 1983).

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 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 ($>2 \mu\text{m}$) increases deposition in the respiratory tract of mice, but decreases deposition in the alveolar region. A linear relationship was found between aerosol dosage of thorium-232 and the amount deposited in the alveolar region (Moores et al. 1980). Approximately twice as much thorium-234 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 (1970b) determined that 1.5-5.0% of the administered amount to rats is absorbed from the lungs 1 day after intratracheal administration of insoluble thorium-232 dioxide. Deposited thorium dioxide tends to remain in the lungs for long periods of time; 68-73% of thorium-232 dioxide 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 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} s after 30 days following intraperitoneal injection in mice were 370.8 mg thorium/kg for soluble thorium-232 nitrate and 589.1 mg thorium/kg for soluble thorium-232 chloride, while 2000 mg thorium/kg for insoluble thorium-232 dioxide resulted in deaths of only 2/18 mice (Syao-Shan 1970b).

Lung levels of thorium (230 and 232) 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. Though intake of thorium through the air may account for less than 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

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to the low gastrointestinal absorption rate (0.02%) in humans (Maletskos et al. 1969; Sullivan et al. 1983).

2.3.1.2 Oral Exposure

ICRP has recommended a human gastrointestinal absorption value of 0.02% for all forms of thorium (ICRP 1979). In a recent review of the literature by Johnson and Lamothe (1989), a human gastrointestinal absorption value of 0.1 to 1% was calculated. Absorption of thorium in the form of thorium nitrate is 40-fold higher in neonatal rats (1.1-1.2%) (Sullivan et al. 1980b, 1983) than in adult rats (0.028-0.5%) (Sullivan et al. 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, or dogs. Solubility factors 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 Pavlovskaja (1973). It was found that the rate of absorption of thorium-EDTA by the gastrointestinal tract was 60 times greater than that of thorium dioxide. Thorium nitrate had a 4 times greater absorption rate 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.

2.3.1.3 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).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

The median concentrations of thorium-232, thorium-230, and thorium-228 in bone and various soft tissues of autopsy samples of a control population from Grand Junction, CO, and Washington, DC are presented in Table 2-4 (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 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 thorium-228 than

TABLE 2-4. The Median Concentrations of Thorium Isotopes in Autopsy Samples from Grand Junction, Colorado, and Washington, DC^a
(in pCi/kg wet weight)

Organ	# of Samples Analyzed	Grand Junction, Colorado			# of Samples Analyzed	Washington, DC		
		Th-228	Th-230	Th-232		Th-228	Th-230	Th-232
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	4.60	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	0.10
Testicles	44	0.02	0.06	0.05	-	-	-	-
Spleen	14	0.06	0.13	0.09	-	-	-	-
Thyroid	1	0.33	0.82	0.65	-	-	-	-

^aSource: Ibrahim et al. 1983; Singh et al. 1983; Wrenn et al. 1981

Th = thorium.

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thorium-232 in bone is that a major portion of the thorium-228 may be from intake of radium-228 (radium appears to be absorbed from the gastrointestinal tract to a greater extent than thorium); radium-228 concentrates in bones and decays to thorium-228 (Wrenn et al. 1981). Studies in mice have shown that thorium-227, injected intraperitoneally, distributes directly to the bone (Miiller et al. 1978); therefore, there may be other explanations for the higher levels of thorium-228 than thorium-232 in the bone. More thorium-232 is retained in the lungs and lymph nodes than thorium-230, suggesting that the solubilization of thorium-230 may be faster than that of thorium-232 in the lungs. This may be due to thorium-230 being inhaled in smaller particles than thorium-232. Consequently, thorium-230 is removed more quickly from the lungs and is transported to bone. The low content of thorium in the reticuloendothelial system (liver, spleen, bone marrow) is in contrast to the distribution following intravenous injection of thorotrast (ThO_2 colloid), where the vast majority of the thorium is taken up by the macrophages of the reticuloendothelial system.

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).

2.3.2.2 Oral Exposure

Autopsy data of persons environmentally exposed to thorium indicated that pulmonary lymph nodes contained the highest levels of thorium (mean 53.4 $\mu\text{g/kg}$), followed by the lungs (mean of 5.4 $\mu\text{g/kg}$, ranging from 1.5-16 $\mu\text{g/kg}$) and bones (mean of 0.55 $\mu\text{g/kg}$, ranging from 0.2-9.0 $\mu\text{g/kg}$) (Sunta et al. 1987). This study estimated that the daily intake of thorium through food, water, and inhalation was 2.29 $\mu\text{g/day}$, with the majority from food and water ingestion (2.27 $\mu\text{g/kg}$). However, it was determined that, since absorption through the gastrointestinal tract is so 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 thorium-232 nitrate was located in the bones of rats.

2.3.2.3 Dermal Exposure

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

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2.3.2.4 Other Routes of Exposure

The majority of thorium studies concern the injection of colloidal thorium-232 dioxide (Thorotrast) into patients as a radiographic contrast medium. Approximately 97% of intravenously injected Thorotrast is taken up by the reticuloendothelial system (RES) and distributed to the liver (59X%), spleen (29%), and bone marrow (9%) (BEIR IV 1988; Kaul and Muth 1978; Kaul and Noffz 1978; Parr et al. 1968; Wegener et al. 1976). Thorium is also deposited in the lymph nodes throughout the body after being transported from the liver and the spleen via the lymph ducts (Wegener et al. 1976). The distribution is inhomogeneous in all tissues and organs since thorium, which is complexed with transferrin in the serum (Peter and Lehmann 1981), is taken up by the macrophages of the RES (Hallegot and Galle 1988; Odegaard et al. 1978). Thorotrast tends to remain in the RES, but some of the radium-228 and radium-224, produced by decay of their parent nuclides, escapes from Thorotrast deposits, possibly as a result of the recoil energy created from decay, and migrates to bone (Kaul and Noffz 1978; Parr et al. 1968). The dose rate to the organs of the RES is dependent upon the nonuniform deposition of Thorotrast aggregates (clumping of the colloid within the organ), the self-absorption of alpha particles in the aggregate itself (alpha particles are absorbed by the aggregate and not by the surrounding tissue), and the characteristic metabolic behavior of thorium daughters (Kato et al. 1979; Kaul and Noffz 1978). Kaul and Noffz (1978) determined that, as the concentration of Thorotrast increases in an organ, alpha self-absorption is increased so that the effective alpha dose to the tissue may be reduced. Kato et al. (1979) found that the value for selfabsorption in fibrous tissue was higher than for nonfibrous tissue and was dose dependent. Mean annual radiation doses from the intravenous injection of 30 mL of Thorotrast were: 30 rads/year in liver, 80 rads/year in spleen, 10 rads/year in red bone marrow, 4.5 rads/year in lungs, and 15 rads/year in the cells on the bone surface. The dose to compact bone was 3.3 rads/year and the dose to cancellous bone was 4.8 rads/year (Kaul and Muth 1978). Due to the uneven distribution of thorium within the colloid, however, these mean annual doses must be considered estimates. The fact that toxic effects rarely appeared in the spleen following Thorotrast injection regardless of the high radiation dose was unexplained, but implies that the liver is more susceptible than the spleen to the effects of radiation and/or Thorotrast. Mays (1978) determined the dose rate to the endosteum (the sensitive cells for the induction of bone sarcoma may lie within 10 μ m of bone surfaces) to be about 16 rad/year (7 rad/year from radium-224 [5.1], thorium-228 [1.5], and radium-228 [0.4] translocated from Thorotrast to calcified bone and 9 rad/year from Thorotrast on bone surfaces [5.9] and in red marrow [3.1]). Kaul and Noffz (1978) estimated that the alpha dose 30 years after injection of 25 mL of Thorotrast would be: 750 rad in liver, 2100 rad in spleen, 270 rad in red bone marrow, 18 rad in total calcified bone, 13 rad in the kidneys, and 60-620 rad in various parts of the lungs.

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The distribution pattern of intravenously-injected Thorotrast in animals is similar to the pattern in humans; most of the Thorotrast is taken up by the RES (Guimaraes et al. 1955; McNeill et al. 1973; Reidel et al. 1979). Reidel et al. (1979) determined that the average percent distribution of Thorotrast in the liver was within one order of magnitude in mice, rats, rabbits, dogs, and humans. The amount of thorium in the spleen of all species, except mice, was clearly below that in humans. Only 50% of the thorium in rats was retained in the liver and spleen, while approximately 85% was retained in humans. Direct comparison of the species is difficult, since the data were taken from other authors and analyzed by Reidel et al. (1979). The study concluded that the biological behavior of colloids was similar in humans and animals. Kaul and Heyder (1972) reported an extremely low rate of clearance of the colloid form from the blood about 1 hour after intravenous injection in rabbits. Subsequently, an increase in the rate of disappearance from the blood of the colloid form (biological half-life of 90 minutes) and of the soluble form (biological half-life of 75 minutes) was found. After 3, 6, or 12 hours, 23, 45, or 60% of the injected amount, respectively, was located in the liver.

Maletskos et al. (1969) found that, following intravenous injection in humans, thorium-234 citrate generally was retained in the skeleton and soft tissues rather than in the RES, as found with Thorotrast. A similar distribution pattern was found in dogs injected intravenously with thorium-228 citrate (Stover et al. 1960). Intravenous exposure studies in rats and guinea pigs, however, showed a distribution of thorium-234 sulfate similar to Thorotrast: 60-68% in the liver, 3-7% in the spleen, 0.4-1% 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 thorium-234 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} ; 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.

2.3.3 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. It has also been determined that thorotrast (ThO_2 colloid) blocks the uptake of labelled protein by the RES in female rabbits and in both male and female rats (Hyman and Paldino 1967). The mechanism of the blockade is not clear. Sex differences were found in rabbits but not in rats. The particle size of the

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Thorotrast colloid influences its effect on the uptake of protein; only particles larger than 1 μm will interfere with uptake of protein by the RES.

2.3.4 Excretion

2.3.4.1 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 thorium-230 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 thorium-230 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 thorium-232 and thorium-230 in the lungs of subjects living in the vicinity of uranium mine tailings (Grand Junction, CO) 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 thorium-232 and thorium-230, 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 isotope from nature apparently is retained in the lungs longer than the 230 isotope.

In a subject who had accidentally inhaled thorium-228 dioxide (alpha emitter, radioactive half-life of 1.9 years), the biological half-life for long-term clearance of thorium-228 from the body was at least 14 years as a result of skeletal deposition (Newton et al. 1981). The early lung clearance of thorium-228 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 (ICRP 1979). Davis (1985), however, concluded that both thorium-232 nitrate and thorium-232 dioxide were class Y compounds by determining the solubility in simulated lung fluid. The near equilibrium of thorium-230, uranium-234, and uranium-238 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 thorium-230/uranium-234 ratio increases with time, suggesting that uranium is cleared faster than thorium from dog lungs (Singh et al. 1986). The effective half-life of inhaled thorium-227 nitrate (radioactive half-life of 18.7 days and biological half-life of about 20 days) in the lungs of rats was found to be about 10 days (Müller et al. 1975). Pavlovskaja et al. (1974a) determined that the excretion of intratracheally-administered thorium-228 (as thorium dioxide or thorium chloride) in the feces occurred

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in two phases in the rat: in the first phase, up to 60% of the thorium-228 contained in the body was eliminated, and in the second phase, the rate of thorium-228 excretion in the feces averaged 0.25% of the body burden daily.

2.3.4.2 Oral Exposure

It was determined in several species of animals (mice, rats, rabbits) that more than 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.

2.3.4.3 Dermal Exposure

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

2.3.4.4 Other Routes of Exposure

A very small percentage of injected thorium-232 dioxide (Thorotrast) in humans was excreted (more in the feces than urine) (Kaul and Muth 1978; Molla 1975). Jee et al. (1967) found that a patient excreted 0.7% of the injected amount of Thorotrast in the 17 days between injection and the death of the patient (mode of excretion not reported). Kemmer (1979) determined that the amount of thoron (radon-220) exhaled by the lungs in humans correlated to the amount of Thorotrast intravenously injected. The thoron (radon-220) correlated with a "radium-224 equivalent value."

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 thorium-234 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 thorium-234 was retained at 100 days after injection, with a biological half-time of more than 5 years (Maletskos et al. 1969).

Less than 5% of thorium was excreted in the urine up to 42 days after intravenous injection of thorium-234 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 thorium-228 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)

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reported the excretion of thorium citrate administered as thorium-234 tracer plus thorium-232 carrier in rats. No differences were found in the rate and 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 quickly cleared from the blood. The higher fecal levels of thorium in the high exposure level animals suggest greater biliary excretion.

2.4 RELEVANCE TO PUBLIC HEALTH

Very little data exist on health effects due to inhalation, oral, or dermal exposure of thorium in humans or animals. The existing health effects data suggest that thorium may pose a potential health threat to an exposed population. Some evidence of respiratory disease and increased incidence of pancreatic, lung, and hematopoietic cancers in humans was found following inhalation exposure (Archer et al. 1973; Polednak et al. 1983; Stehney et al. 1980). These effects were seen in thorium workers exposed to many toxic agents, so that the effects cannot be attributed directly to thorium exposure, but a causal effect cannot be discounted. High incidences of malignancies found in patients injected intravenously with colloidal thorium (Thorotrast) demonstrates the carcinogenic potential of thorium. Subchronic animal studies have shown pneumocirrhosis and increased incidences of lung cancer following inhalation exposure (Likhachev et al. 1973a). No studies regarding the health effects to humans from oral or dermal exposure were reported in the literature. Animal studies of oral exposure to thorium showed death at high exposure levels, but no other systemic effects were observed (Patrick and Cross 1948). Animal pharmacokinetic data suggest that, while soluble forms are absorbed to a greater extent than insoluble forms, no chemical form of thorium is absorbed appreciably from the gastrointestinal tract (Pavlovskaja 1973; Sullivan et al. 1980a, 1980b, 1983). Dermal-administered thorium nitrate in animals showed effects on the skin, the testes, and sperm morphology when administered directly on the scrotum, but no other systemic effects were observed (Tandon et al. 1975).

The chemical form of thorium (soluble or insoluble) inhaled, ingested, or injected determines the absorption distribution and excretion of thorium into the body and, consequently, the toxic effects. Thirty-three percent of inhaled thorium citrate and 19% of inhaled thorium chloride was absorbed from the lungs of rats (Boecker et al. 1963), while 1.5-5.0% of insoluble thorium dioxide was absorbed following intratracheal administration in rats (Syao-Shan 1970b). Following ingestion of thorium, soluble chemical forms were absorbed 4 (thorium nitrate), 10-20 (thorium chloride) or 60 (thorium-EDTA) times greater than insoluble thorium dioxide (Pavlovskaja 1973). The fact that the LD₅₀s of these thorium compounds increase with

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solubility in a similar pattern, thorium dioxide <<< thorium nitrate < thorium chloride (Syao-Shan, 1970b), indicates that solubility and acute toxicity are closely related. The less soluble forms of thorium, however, are of greater radiological concern because they remain in the body for long periods of time. Thorium dioxide is retained in the body for long periods of time after inhalation (Newton et al., 1981), and the long-term radiation effects from thorium dioxide, as evidenced by the induction of cancer by intravenously injected Thorotrast, are apparently of greater concern than from the more soluble (and readily excreted) forms of thorium.

The organ distribution of the thorium isotopes was similar in humans and dogs, with the skeleton having the highest levels of thorium (Singh et al. 1988). In both humans and dogs, the level of thorium-232 > thorium-230 > thorium-228 in the lungs. The average skeletal activity of thorium-228 was 30-50 times greater than thorium-232 in dogs, but the difference was only 4- to 5-fold in humans. The higher levels of thorium-228 in dogs compared to humans may be due to a higher intake of radium-228 in their diet (Singh et al. 1988). Radium-228 will translocate to bones and decay to thorium-228. In this study, dogs had been exposed in the food, water, and air to simulate human exposure. Wrenn et al. (1983) reported that thorium-230, uranium-234, and uranium-238 were in close equilibrium in the lungs of humans, while they were in disequilibrium in the lungs of dogs (thorium-230/uranium-234 ratio averaged 6.3). The data suggest that, under these experimental conditions, uranium is cleared faster than thorium from dog lungs (Wrenn et al. 1983). These species differences have been proven not to be due to radiochemical methods (Singh et al. 1986), but may be due to time factors or to a particle size difference, as the experimental animals and the uranium miners inhaled aerosols of different composition and size.

The vast majority of the human thorium data deal with the effects of Thorotrast (colloidal thorium-232 dioxide) administered intravenously to patients as a radiologic contrast medium. The literature suggests that the toxic effects of Thorotrast are due to the alpha radiation effects of thorium and not to the chemical effects of thorium or of the colloid (BEIR IV 1988; Taylor et al. 1986). Cirrhosis of the liver, hepatic tumors, and blood dyscrasias were the most common effects of intravenously injected Thorotrast. Because Thorotrast is no longer used in this capacity, the introduction of new health risks from injection of Thorotrast is not considered a problem. Although the pharmacokinetic behavior of intravenously injected Thorotrast in the body is vastly different from the behavior of inhaled or ingested thorium, and the injected Thorotrast was sometimes enriched with a higher proportion of more radioactive isotopes of thorium (e.g., thorium-230 or thorium-228) than is generally found in the environment, the effects from Thorotrast in patients suggest that thorium could be a potential carcinogen (BEIR IV 1988).

The main issue regarding thorium is its potential radiological effect. Since thorium is an alpha-emitting bone-seeker, the small amount of thorium that enters the body migrates to bone surfaces. The carcinogenic potential

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of thorium is most likely a result of its radiological properties. Different isotopes of thorium have different radioactive half-lives: thorium-232 (natural thorium) is a long-lived alpha emitter (half-life of 1.4×10^{10} years), thorium-230 is a relatively long-lived alpha-emitter that is a member of the uranium decay series (half-life of 8×10^4 years), thorium-228 is a short-lived alpha-emitter that is a member of the thorium series (half-life of 1.9 years), and thorium-234 is a short-lived beta-emitter that is a member of the uranium series (half-life of 24.1 days).

For short-term experiments, thorium-232 is considered radiologically inert since its half-life is so long. Therefore, the chemical toxicity of thorium was tested using this isotope. The low chemical toxicity of thorium was evidenced by the lack of initial systemic effects in patients injected with Thorotrast and in occupationally exposed workers. Animal studies also showed low toxicity (Guimaraes et al. 1955; Patrick and Cross 1948). Natural thorium (thorium-232) is toxic only after a latency period of 20-30 years, when the radiological effects are manifested.

The radiological effects of thorium were examined by testing isotopes with shorter radioactive half-lives than thorium-232. No increased mortality was found in mice injected intravenously with 0.5 mL Thorotrast (3660 mg thorium-232/kg) (Guimaraes et al. 1955), or in dogs after intraarterial injection of thorium nitrate (476 mg thorium-232/kg), but the LD_{50} for intravenously-injected thorium-230 in rats was 42.7 mg thorium/kg (Boone et al. 1958). The toxic effects of thorium were attributed to radiological and not chemical effects (Boone et al. 1958).

The removal of thorium from the body has been achieved by the use of chelating agents, primarily ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA) (Fried and Schubert 1961; Peter-Witt and Volf 1984, 1985; Young and Tebrock 1958). In animals, DTPA was about 10 times as effective at removing thorium from the body as EDTA, and Ca-DTPA was more effective than Zn-DTPA (Fried and Schubert 1961; Peter-Witt and Volf 1985). The total percentage of thorium removed from the body using chelation therapy was not reported. Thorium administered in the monomeric form (single molecule) was cleared more effectively from the body than when given in the polymeric form (colloidal). The polymeric form was deposited primarily in the liver and the level was only lowered when massive, nearlethal amounts of chelating agent were given (Fried and Schubert 1961). The chelating agents were most effective shortly after thorium dosing (Young and Tebrock, 1957).

Death. No deaths in humans resulting from acute inhalation, oral, or dermal exposure to thorium have been reported. Deaths from various forms of cancers have been observed (liver tumors, leukemia, bone tumors), however, in patients injected intravenously with Thorotrast (Thorotrast was enriched with more active forms of thorium than are environmentally available) (BEIR IV 1988). The toxicity of thorium depends on the specific isotope (dose rate effect: isotopes with shorter radioactive half-lives and higher energy

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are more toxic after intravenous injection [Boone et al. 1958] and the chemical form of thorium (total dose effect: soluble compounds are more toxic than insoluble compounds after intraperitoneal injection [Syao-Shan 1970b]). Intravenous and intraperitoneal injections, however, are not normal routes of environmental exposure. No deaths were reported in animals following inhalation exposure, and high exposure levels were necessary to produce death in animals following oral exposure, since gastrointestinal absorption is very small (0.02%). The acute exposure levels required to cause death in humans are not known and cannot be predicted based on the animal data.

Systemic Effects. There is evidence in the literature of an increase in respiratory disease (SMR=1.31) (Polednak et al. 1983) and hepatic effects (increase in serum levels of aspartate aminotransferase, globulin, and total bilirubin) (Farid and Conibear 1983) in individuals occupationally exposed to thorium. The individuals, however, were occupationally exposed to other toxic substances (uranium dust) as well as other sources of radioactivity, so that these effects cannot be attributed directly to thorium. Both studies suggest that the observed effects may have resulted from radiological toxicity. Progressive cirrhosis of the lungs was observed in rats subchronically exposed by inhalation to thorium dioxide (Likhachev et al. 1973a). The severity of the lung cirrhosis was related directly to the radiation dose and treatment, but the exact radiation exposure level was not reported. Effects on hematological parameters, suggestive of radiological toxicity, were found in dogs subchronically exposed by inhalation to various chemical forms of thorium (Hall et al. 1951). No other systemic effects were observed in animals exposed by inhalation, and no systemic effects were found in orally or dermally exposed animals.

Following intravenous injection of Thorotrast, cirrhosis of the liver was the primary systemic effect in humans and animals. Hematological disorders (aplastic anemia, leukemia, myelofibrosis, and splenic cirrhosis), cardiovascular effects (myocardial infarction, severe coronary luminal narrowing and internal alteration of the carotid artery), and Thorotrastoma (localized fibrosis surrounding deposits of Thorotrast) were also found in patients injected with Thorotrast. The effects of Thorotrast were a result of the radiological toxicity of thorium.

The existing data indicate that, in humans, respiratory and hepatic effects result from inhalation exposure and that the liver, hematopoietic system and cardiovascular system are the target organs following intravenous injection of Thorotrast. Studies in animals have not reported effects in these tissues, with the exception of the liver, further supporting the concern that the humans were exposed to other toxic agents, thereby preventing an accurate assessment of the systemic toxicity of thorium.

Immunological Effects. Studies in humans or animals were not located regarding the immunological effects of thorium following oral and dermal exposure. No histopathological effects were found in the lymph nodes of

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animals exposed by inhalation to thorium dioxide (Hodge et al. 1960). Following injection of Thorotrast in humans, fibrosis of the lymph nodes and the spleen were observed (da Silva Horta 1967a; Wegener and Wesch 1979; Wegener et al. 1976). A suppression of immune response was found in mice following intravenous and intraperitoneal injection of Thorotrast (Michael and Murray 1970). Thorotrast affected lymphoid cells involved in antibody formation and blocked phagocytic cells in organs of the RES. In the absence of data via relevant routes of exposure, the immunotoxic potential of thorium cannot be fully assessed.

Neurological Effects. There have been no human or animal studies specifically designed to determine the neurological effects of thorium. Neurological effects, such as narcosis, ataxia, or cholinergic signs, have not been reported in any of the inhalation or oral studies in animals. It is not known whether humans would experience major neurological deficits from exposure to thorium.

Developmental Effects. There have been no human or animal studies regarding the developmental effects of thorium following any relevant route of exposure (inhalation, oral, dermal). Since information regarding developmental effects in animals are not known, conclusions regarding the potential for developmental effects in humans are not known.

Reproductive Effects. No studies were located regarding reproductive effects in humans or animals following inhalation or oral exposure to thorium. When thorium was applied directly to the scrotum of rats, mild edema of the seminiferous tubules and the interstitium and desquamation of sperm and giant spermatid-type cells were observed (Tandon et al. 1975). Since information is limited to one study in one species and one sex, and since no information on the effect of thorium on reproductive function was located, conclusions regarding the potential for humans to develop these effects are not known.

Genotoxic Effects. Chromosomal aberrations have been found in the lymphocytes of Thorotrast patients and occupationally exposed workers (Fischer et al. 1967; Hoegerman and Cummins 1983; Kemmer et al. 1971, 1979). A study by Nishioka (1975) screened thorium chloride (0.05 M) as a potential mutagen by determining whether it inhibited bacterial growth. Since bacterial growth was not inhibited, thorium was not further tested for mutagenicity. Thorium chloride (10%) was shown to have no effect on the survival of Klebsiella oxytoca or Klebsiella pneumoniae (Wong 1988). Based on the limited human data, thorium appears to be a genotoxic agent.

Cancer. Increased incidences of lung, pancreatic, and hematopoietic cancers were observed in individuals occupationally exposed to thorium (Archer et al. 1973; Polednak et al. 1983; Stehney et al. 1980). The individuals were occupationally exposed to other toxic substances (uranium dust) as well as other sources of radioactivity; hence, the higher incidences of cancer cannot be attributed directly to thorium. The follow-

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up period in the studies ranged from 17-35 years, and the latency periods of the various types of cancer were not reported. In rats chronically exposed by inhalation to thorium as thorium dioxide, lung tumors were found that correlated with the total radioactivity in the lungs (Likhachev 1976; Likhachev et al. 1973b). The exact amount of administered radioactivity was not reported. No studies in humans were located regarding oral or dermal exposure to thorium. No malignancies were reported following oral or dermal exposure of rats to thorium, but these studies were of relatively short duration (oral study, 4 months; dermal study, 15 days) and were not designed to detect an increase in the incidence of neoplasms.

Following intravenous injection of Thorotrast in humans and animals, various malignancies were found, primarily liver cancers (latency period of 25-30 years), leukemia (latency period of 20 years), and bone cancers (latency period of about 26 years). Short-lived daughter products of thorium also resulted in the induction of bone sarcoma because of their short radioactive half-lives. Intravenous injection of thorium-228 resulted in dose-dependent induction of bone sarcoma in dogs (Lloyd et al. 1985; Mays et al. 1987; Stover 1981; Wrenn et al. 1986). At the highest administered level, the animals died from systemic radiological effects (e.g., radiation induced blood dyscrasia and nephritis) before the bone sarcoma could develop (Stover 1981; Taylor et al. 1966). A relationship was found between the amount of thorium-227 (half-life of 18.7 days) injected intraperitoneally and the incidence of bone sarcoma in mice (Luz et al. 1985; Miiller et al. 1978).

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers 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 or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc

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and selenium). Biomarkers of exposure to thorium are discussed in Section 2.5.1.

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 often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by thorium are discussed in Section 2.5.2.

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. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Thorium

Exposure to thorium can be determined by measurement of radioactive thorium and/or daughters 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 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.

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2.5.2 Biomarkers Used to Characterize Effects Caused by Thorium

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. For further information on the health effects of thorium, see Section 2.2 of Chapter 2.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Thorium is commonly found in combination with other actinide elements, with organic and inorganic chemicals, and with acids and bases during occupational exposure. The health effects of occupational exposures to thorium on humans, therefore, cannot necessarily be attributed to thorium. The daughter products of thorium have unique properties that also add to the radiological toxicity of thorium. For further information, see the toxicological profiles on uranium, radon, and radium.

The injection of tetracycline either before or simultaneously with injection of thorium-228 markedly reduced the deposition of thorium-228 in rat bone to about 60% of control values (Taylor et al. 1971). The effects of tetracycline injection following injection of thorium-228 were not reported. Studies with a similar actinide element, plutonium, suggest that a thorium-tetracycline complex may be formed, which is excreted rapidly through the kidneys. Similarly, chelating agents such as EDTA and DTPA can remove some thorium from the body (see Section 2.4).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Neonatal animals have been found to absorb 20-40 times more thorium through the gastrointestinal tract than adult animals (Sullivan et al. 1980a, 1980b, 1983) indicating that children may be more susceptible to both the chemical and radiological effects of thorium than adults.

2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of thorium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of thorium.

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The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substancespecific research agenda will be proposed.

2.8.1 Existing Information on Health Effects of Thorium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to thorium are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of thorium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

The effects of thorium in humans have been well studied following intravenous exposure, but not following any relevant routes of exposure (inhalation, oral, dermal). Several case studies exist on the effects on thorium millers, especially on the genotoxic and carcinogenic effects of the agent. No studies on the effects of pure thorium on humans have been found by any route of exposure (the thorium miners were exposed to many toxic agents in addition to thorium, and it is impossible to directly attribute effects to thorium). The effects of thorium in animals following intravenous injection have been well studied, but very few studies have been done by a relevant route of exposure. Figure 2-3 reflects the few studies regarding oral and dermal exposure of animals to thorium located in the existing literature.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. No studies were located regarding the effects of thorium in humans following acute exposure by any relevant route. Intravenous injection of thorium as an x-ray contrast medium into people resulted in death from various malignancies 20-30 years following injection. Animals studies were limited to determining dose levels resulting in death following inhalation and oral exposure, and in dermal and reproductive effects following dermal administration to the lateroabdominal and scrotal skin. Inhalation-based pharmacokinetic data indicate that the lymph nodes, lungs, and bone may be the target organs of thorium toxicity. Oral pharmacokinetic data indicate that bone may be the target organ of toxicity following ingestion of thorium. The acute toxicity of thorium in animals has also been tested by routes of exposure (intravenous, intraperitoneal, intratracheal) that are difficult to interpret, and it would be useful to compare these toxic levels to toxic levels found after administration by a relevant route (inhalation, oral, dermal). Knowledge about the acute toxicity of thorium is important because people living near hazardous waste sites might be exposed for brief periods.

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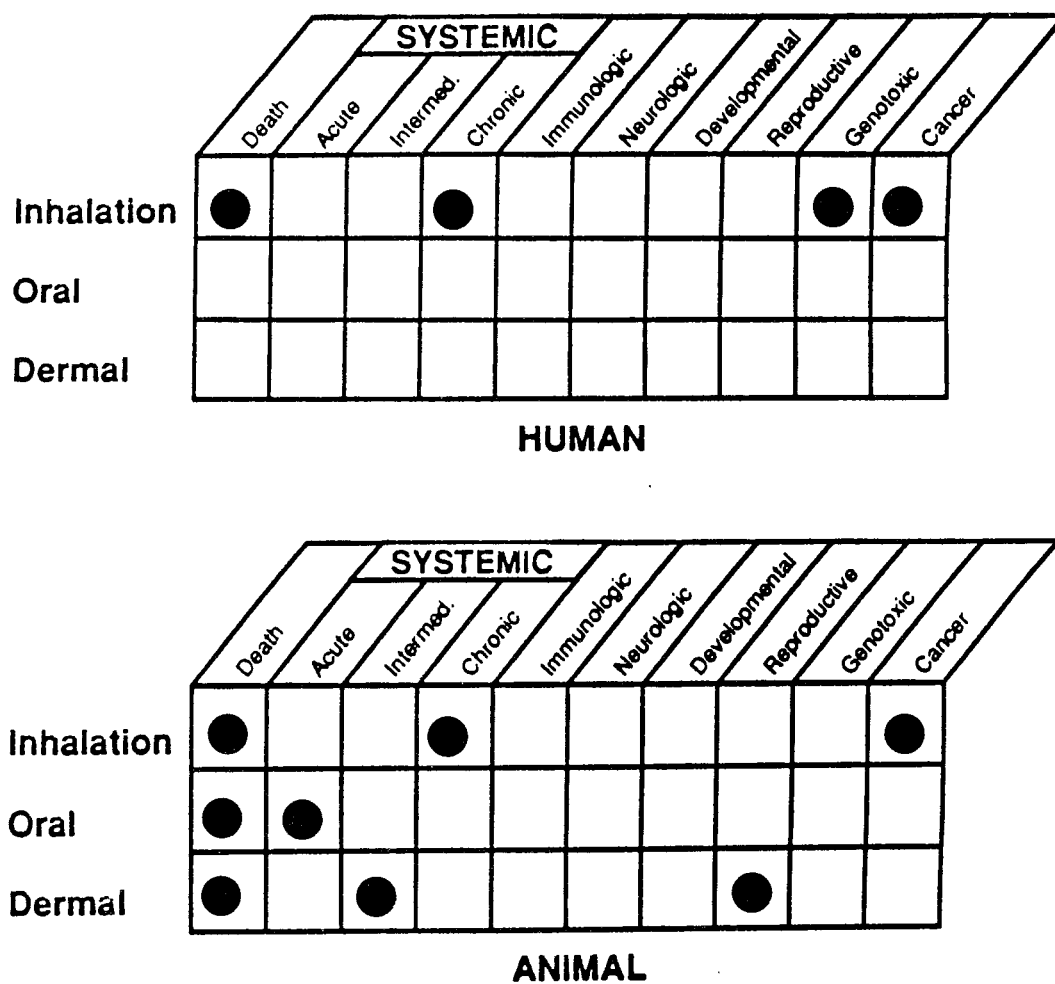


FIGURE 2-3. Existing Information on the Health Effects of Thorium

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Intermediate-Duration Exposure. No studies were located regarding the effects of thorium in humans following intermediate-duration exposure by any route of exposure. Two animal studies were reported: one inhalation study in rats showing lung damage and one oral study in mice resulting in death. Intermediate-duration dermal studies in animals were not located. The lungs appear to be the target organs following intermediate-duration inhalation exposure to thorium. Oral pharmacokinetic data indicate that bone may be the target organ of toxicity following ingestion of thorium. More extensive studies by all relevant routes (inhalation, oral, dermal) would be useful in assessing both the chemical and radiological toxicity of thorium. Intermediate-duration toxicity information is important because people living near hazardous waste sites might be exposed for corresponding time periods.

Chronic-Duration Exposure and Cancer. Several studies have been reported regarding the toxic effects on workers occupationally exposed to thorium or monazite sand found in refinery dust. In these studies, effects on the lungs and chromosomes and an increased cancer incidence were reported. Because the workers were exposed to many toxic agents, however, effects cannot be attributed directly to thorium. Epidemiology studies investigating workers exposed primarily to thorium (e.g., during the production of gas lamp mantles) would be useful. No human studies were located regarding chronic oral or dermal exposure. Many studies on longterm radiological effects of thorium have been reported following intravenous injection of thorium dioxide in the form of Thorotrast in both humans and animals. Effects reported in these studies included cirrhosis of the liver, hematological disorders, and various malignancies. Studies have shown that the lungs and the hematological system are the target organ systems for thorium toxicity. Oral pharmacokinetic data indicate that bone may be the target organ of toxicity following ingestion of thorium. Chronic studies by relevant routes of exposure, inhalation and oral, are important because people living near hazardous waste sites might be exposed to thorium for years.

Studies in workers occupationally exposed to thorium have reported an increase in the incidence of pancreatic, lung and hematopoietic cancers. These effects were observed in workers exposed to many toxic agents, so they cannot be attributed directly to thorium. Intermediate duration inhalation exposure of rats to thorium dioxide resulted in lung tumors. No data were located regarding the carcinogenic effects of oral or dermal thorium exposure in humans or animals. Further chronic exposure studies by all relevant routes of exposure (inhalation, oral, dermal) using wider exposure level ranges and a number of species of animals may be useful in assessing the carcinogenic potential of thorium in humans.

Genotoxicity. Occupationally exposed workers as well as patients injected with Thorotrast show chromosomal abnormalities in their lymphocytes. No in vivo genotoxicity studies in animals or in vitro studies

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in bacterial strains were located, but these studies may be useful in determining whether thorium has the potential to cause gene mutations in addition to chromosomal abnormalities.

Reproductive Toxicity. No studies were located regarding the reproductive effects of thorium in humans following exposure by any route. Neither inhalation nor oral reproduction studies in animals were located. Pharmacokinetic data following inhalation or oral exposure were not located to allow the prediction of possible reproductive effects. One dermal rat study found testicular effects after administration directly onto the scrotal skin. Additional inhalation, oral, and dermal reproduction studies and multigenerational studies would be helpful in assessing the potential risk to humans.

Developmental Toxicity. No studies were located regarding the developmental effects of thorium in humans or animals following exposure by any route. Also, pharmacokinetic data do not exist that may predict whether thorium crosses the placental barrier. Further developmental studies in animals by all relevant routes of exposure may clarify the potential developmental effects of thorium in humans.

Immunotoxicity. No studies were located regarding the immunological effects of thorium in humans or animals following any relevant route of exposure (inhalation, oral, dermal). One report, however, showed intraperitoneal and intravenous injection of thorium dioxide in mice resulted in a suppression of the immune response. Studies on the immunotoxic effects of thorium, both histopathological and effects on the immune response, by all relevant routes of exposure in animals may determine the potential immunotoxic effects in humans.

Neurotoxicity. No studies were located regarding the neurological effects of thorium in humans or animals following exposure by any route. Other metals, such as lead, however, have been shown to have more severe neurological effects on children than adults; therefore, it is possible that children may be more susceptible than adults to the effects of thorium. Studies on the neurological effects of thorium, both histopathological and effects on behavior by all relevant routes of exposure in animals, may determine the potential neurological effects in humans.

Epidemiological and Human Dosimetry Studies. Epidemiology studies have investigated the relationship between long-term exposure to thorium and systemic effects, genotoxic effects, and cancer in humans. The authors of these studies found increases in respiratory disease and certain types of cancer (lung, pancreatic, hematopoietic) in exposed thorium workers, but the findings were not definitive. The existing epidemiological studies are often weakened by not sufficiently accounting for smoking habits or exposure to other chemicals and by relying too heavily on the accuracy of death certificates. Increased incidences of chromosomal abnormalities were found in exposed workers (approximately 4% dicentric in controls vs. 20% in

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exposed workers) as well as in patients injected intravenously with colloidal thorium dioxide (Thorotrast) (1-25 dicentric per 100 cells). The occupational studies focus primarily on adult males. It would be useful to study groups that include women, children, and neonates that have been exposed to greater than normal levels of thorium to determine their level of susceptibility. Epidemiology studies investigating workers exposed primarily to thorium (e.g., during the production of gas lamp mantles) would also be useful. Further studies assessing the cause/effect relationship between thorium exposure and human health effects would be helpful in monitoring individuals living near a hazardous waste site.

Biomarkers of Exposure and Effect. The major route of excretion of inhaled or ingested thorium is in the feces. Exposure to thorium can be determined by measurement of thorium and/or its daughters in the feces, urine, blood, or expired air. The body burden of thorium may be estimated by the measurement of external gamma rays emitted from thorium daughters in the body. Further studies correlating thorium exposure with thorium and/or thorium daughters in the urine, feces, blood, and expired air would be helpful in more accurately quantifying thorium exposure.

No relationship was found between the measured body burden of thorium and complete blood count parameters (e.g., hemoglobin, red and white blood cells) in humans occupationally exposed to thorium (see Section 2.2.1.2). Further studies may reveal thorium-specific biomarkers that may alert health professionals to thorium exposure before toxicological effects occur.

Absorption, Distribution, Metabolism and Excretion. The absorption of thorium from the lungs and the gastrointestinal tract and the tissue distribution of thorium have been studied in both humans and animals. Inhalation was found to be the major route of exposure with gastrointestinal absorption being very low (see Section 2.3.1). The data in humans correlate well with the animal data. The excretion of systemic thorium in humans has not been extensively studied, especially the partition between feces and urine, and work in this area in both humans and animals would be helpful. No studies were located regarding the pharmacokinetics in humans or animals following dermal exposure to thorium. Studies on the dermal route of exposure may be helpful in determining whether thorium is a human health hazard by this route.

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2.8.3. On-going Studies

No on-going studies were located relating to the toxicity of thorium in humans or animals.