CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of thorium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to thorium, but may not be inclusive of the entire body of literature.

Summaries of animal inhalation studies are presented in Table 2-1 and Figure 2-2. Summaries of animal oral studies are presented in Table 2-2 and Figure 2-3. Summaries of animal dermal studies are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration 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 doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be

classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

There are limited data available on the toxicity of thorium following inhalation, oral, or dermal exposure. A few studies examined thorium workers, presumably exposed via inhalation; however, the studies poorly controlled for cigarette smoking and exposure to other toxic compounds. The available laboratory animal data provide some suggestive evidence of gastrointestinal, hematological, and reproductive effects. Signs of gastrointestinal irritation (retching, gagging, and vomiting) were observed in dogs exposed to airborne thorium tetranitrate. Alterations in erythrocytes and/or leukocytes were observed in dogs following exposure to airborne thorium nitrate, thorium oxalate, or thorium tetrafluoride. Edema of the seminiferous tubules were observed in rats following dermal applications to scrotal skin.

There is considerable information on the toxicity of Thorotrast, a colloidal solution of thorium dioxide which was administered intravascularly to visualize vascular structures. A number of these patients have been followed for decades. Observed effects include liver disease, blood disorders, hematopoietic cancers, and bile duct and gall bladder cancers.

Thorium is a metallic element that exists only as radioactive isotopes. A total of 31 thorium isotopes are recognized by physicists ($^{208–238}$Th). Most are manmade, but six isotopes ($^{227, 228, 230, 231, 132, 234}$Th) occur naturally as components of the ^{238}U series, ^{232}Th series, and ^{235}U series (see Figure 4-1). Isotopes in the ^{232}Th series (^{228}Th, ^{232}Th) comprise 99.9% of the naturally-occurring thorium in the environment; isotopes in the ^{238}U series (^{230}Th, ^{234}Th) comprise the remainder of naturally-occurring thorium. All thorium isotopes emit alpha or beta particles with or without gamma radiation (NNDC 2018; Weast 1983) as they decay primarily toward isotopes of lead (Pb). Thorium isotopes vary with respect to decay rates (e.g.,

specific activities) and the various decay chain isotopes produced (see Chapter 4). This toxicological profile for thorium includes chemical, radiological, and physical information for elemental thorium (Th), thorium dioxide (ThO_2), thorium nitrate tetrahydrate ($Th(NO_3)_4 \cdot 4H_2O$), thorium fluoride tetrahydrate ($ThF_4 \cdot 4H_2O$), and thorium carbonate ($Th(CO_3)_2$). Health effects data are available for thorium dioxide, thorium nitrate, and thorium fluoride. Uptake and disposition of thorium in the body (and, hence, the potential for specific health effects from internalized thorium) depend upon the chemical properties of the particular thorium compound to which one may be exposed, as well as the route of exposure (see Section 3.1 for more information regarding uptake and disposition of thorium). Available toxicokinetic, radiological, and health effects data for thorium have not been useful in determining whether thorium toxicity is attributable to radiological, chemical, or combined radiological and chemical properties. Exposure to thorium compounds in amounts large enough to pose a serious chemical health risk would be expected to pose a radiation health risk as well, particularly within lungs where insoluble thorium compounds may be retained and in other tissues where absorbed thorium is retained (e.g., liver, bone).

Alpha particle radiation is the type of radiation from thorium in nature that is of greatest health concern. The equilibrium rate of emission of alpha particles and gamma rays from thorium is very low because the decay rates are limited by the decay rates of the parent radionuclides, which range from 7.1×10^8 to 1.4×10^{10} years. Alpha particles are unable to deeply penetrate skin, but can travel short distances in the body (about 4–6 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 (see Chapter 4). The decay rate or activity of radioactive elements has traditionally been specified in curies (Ci). One curie is the quantity of radioactive material in which approximately 37 billion atoms disintegrate (decay) per second (3.7×10^{10} dps). In international usage, the S.I. unit (the International System of Units) for activity is the Becquerel (Bq), which is the quantity of radioactive material in which 1 atom disintegrates per second (1 Bq = 27 pCi). In animal studies, thorium exposure levels (typically expressed in units of mg thorium/m^3 in air for inhalation studies or mg thorium/kg body weight/day for oral studies) have been converted to activity units (nCi/m^3 or nCi/kg/day; based on the specific activity of a given thorium compound) for presentation in Chapter 2. The specific activity of ^{230}Th is 7.4×10^8 Bq/g (0.02 Ci/g); the specific activity of ^{232}Th is 4,080 Bq/g (1.1×10^{-7} Ci/g).

Once thorium is internalized, it is distributed and excreted at a rate of transfer that is dependent on age. The internal radiation dose from thorium is actually a measure of the amount of energy that the alpha, beta, and gamma emissions deposit in tissue. The short-range alpha and beta radiation produce higher localized doses than longer-range gamma radiation that deposits smaller amounts of energy throughout

the body. Molecular damage results from the direct ionization of atoms that are encountered by alpha radiation, from the indirect ionization of atoms by gamma- and x-rays, and by interactions of resulting free radicals with nearby atoms (free radicals are atoms or groups of atoms containing at least one unpaired electron and existing for a brief period of time before reacting to produce a stable molecule). Tissue damage results when molecular damage is extensive and not sufficiently repaired in a timely manner.

Three primary terms used in assessing radiation dose and health effects are absorbed dose, equivalent dose, and effective dose. In radiation biology, the term absorbed dose refers to the amount of energy deposited by radiation per unit mass of tissue, expressed in units of rad or gray (Gy). An energy deposition of 1 joule/kg = 1 Gy = 100 rad (see Appendix D for a detailed description of principles of ionizing radiation). The equivalent dose (in unit of Sievert or Sv) is the biologically effective dose; it is the absorbed dose multiplied by a radiation weighting factor that is specific to the radiation type. The equivalent dose (H) from internalized thorium radionuclides is estimated using the quantity of material entering the body (via ingestion or inhalation), the biokinetic parameters for thorium (retention, distribution, and excretion), the energies and intensities of the alpha, beta, and gamma radiations emitted, and the parameters describing the profile of absorbed radiation energy within the body. If, for example, a person ingests a given activity of ^{232}Th, the tissues of the body will absorb some or all of the energy of the emitted alpha, beta, and gamma radiation in a pattern reflecting the kinetics of distribution and elimination of the ingested ^{232}Th, the rate at which the radioactive isotope decays to a stable form, and age and other individual parameters for the person during the period in which the radionuclide remains in the body (which affects both the biokinetics of the thorium as well as the potential length of time over which the tissues can be exposed to the radiation). Each tissue and organ, therefore, can receive a different equivalent dose. The effective dose (also measured in units of Sv) is an assessment of the risk of cancer induction from an equivalent dose. Effective dose is estimated by multiplying the equivalent dose by the tissue-specific weighting factor for that organ or tissue, and then adding the various components. This makes effective dose an estimate of the uniform, entire-body risk of developing cancer. It places non-uniform body exposure on the same scale as uniform irradiation with respect to overall cancer induction risk.

The U.S. Environmental Protection Agency (EPA) has published a set of internal dose conversion factors for reference persons of various ages (newborn; 1, 5, 10, or 15 years of age; and adult) in its Federal Guidance Report No. 13 supplemental CD (EPA 1999). These values were updated by Oak Ridge National Laboratory in 2014 (DOE 2014a, 2014b). Age-specific dose coefficients for inhalation and

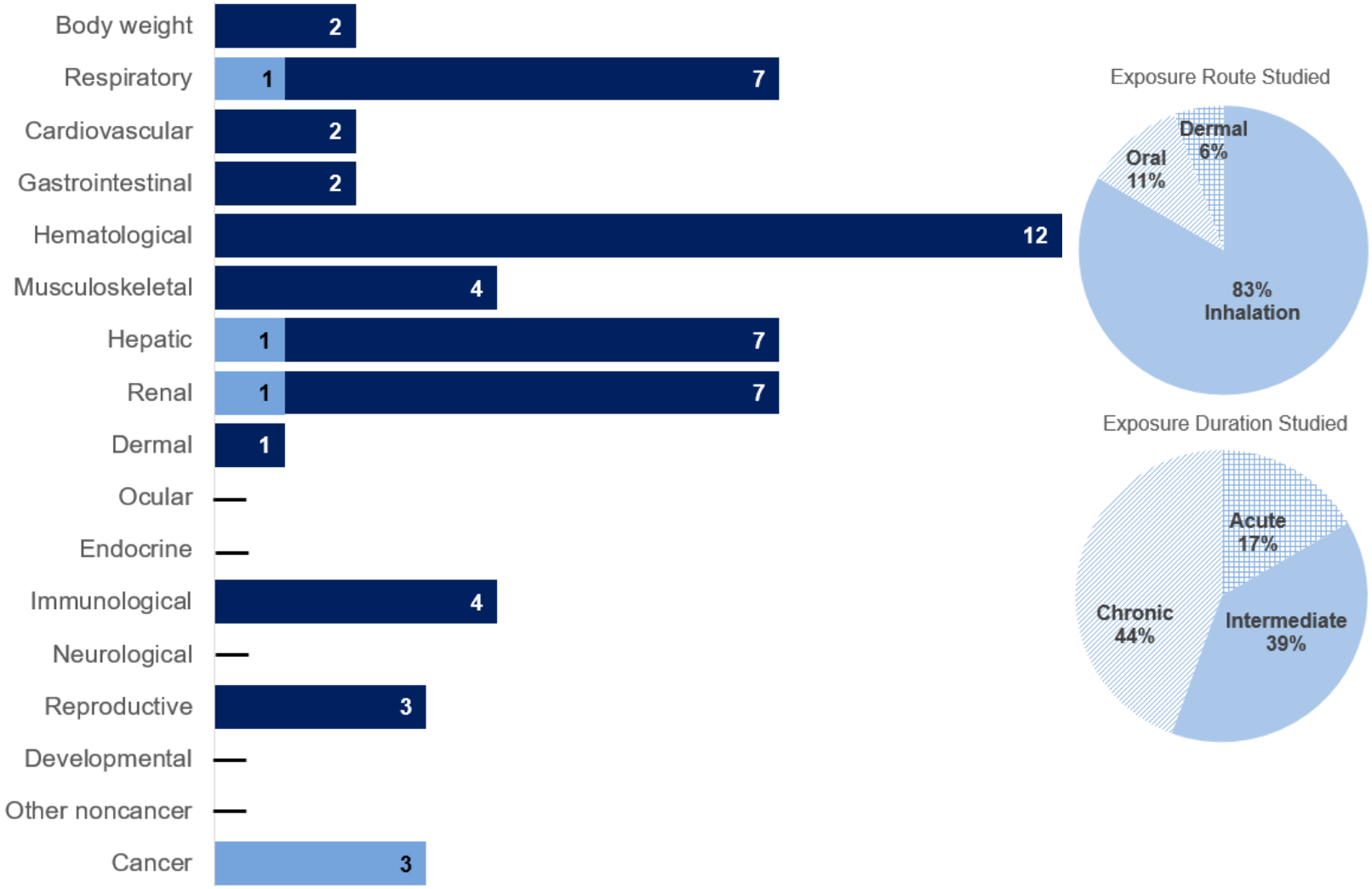
ingestion of any of the radioactive isotopes of thorium by the general public also can be found in International Commission on Radiological Protection (ICRP) publications 67 (ICRP 1994a), 71 (ICRP 1995), and 72 (ICRP 1996) and compiled in Publication 119 (ICRP 2012). Dose coefficients for inhalation, ingestion, and submersion in a cloud of thorium radionuclides can be found in EPA Federal Guidance Report No. 11 (EPA 1988b). Dose coefficients for external exposure to radioisotopes of thorium in air, surface water, or soil contaminated to various depths can be found in EPA Federal Guidance Report No. 12 (EPA 1993) as well as ICRP Publication 116 (2010).

Either a large or small amount of radiation can be damaging to health. Current scientific consensus is that radiation can also increase the probability of cancer, and the current assumption is that 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 low levels of radiation, and since the average individual is exposed to significantly more diagnostic medical radiation than environmental radiation without obvious adverse health impact, the minimum amount of additional radiation that may constitute a health hazard is not well known.

Sections 2.2–2.19 summarize the health effects associated with thorium. Section 2.21 summarizes information regarding health effects of Thorotrast, a colloidal suspension of $^{232}ThO_2$ that was medically injected into patients' veins or arteries worldwide from the late 1920s until the early 1950s as a contrast medium for radiographic procedures, particularly to visualize vascular structures following its intravascular injection. This information is not summarized in Sections 2.2–2.19 because Thorotrast was not a substance found in the environment, was administered via an unnatural route not relevant to environmental exposure of human toxicity concern, and Thorotrast distributed within the body unlike the other thorium compounds to which individuals would be exposed. However, the health effects associated with Thorotrast demonstrate the hazard of alpha radiation to tissues where Thorotrast was retained.

Figure 2-1. Overview of the Number of Studies Examining Thorium Health Effects

Most studies examined the potential hematological, respiratory, hepatic and renal effects of thorium
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 57 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Thorium – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (nCi/m^3)	Parameters monitored	Endpoint	NOAEL (nCi/m^3)	Less serious LOAEL (nCi/m^3)	Serious LOAEL (nCi/m^3)	Effect
ACUTE EXPOSURE									
1	Dog (NS) 4 F	10 exposures 5 days/week 6 hours/day	4.0	BW, GN, HP, BC, UR	Death				No deaths reported
					Hemato		4.0		Leukocytosis, abnormal lymphocytes, and hypersegmented polymorphonuclear granulocytes; no changes in RBC counts
Thorium nitrate tetrahydrate									
Hall et al. 1951									
2	Dog (NS) 4 F	10 exposures 5 days/week 6 hours/day	4.8	BW, GN, HP, BC, UR	Death				No deaths reported
					Hemato		4.8		Decreased RBC, increased percentage of lymphocytes and nonfilamented polymorphonuclear neutrophils
Thorium dioxide									
Hall et al. 1951									
3	Rabbit (NS) 3 M, 3 F	10–11 exposures 5 days/week 6 hours/day	M: 3.8, F: 3.5	BW, GN, HP, BC, UR	Death				No deaths reported
					Hemato	3.8 M 3.5 F			No change in RBC counts
Thorium nitrate tetrahydrate									
Hall et al. 1951									
INTERMEDIATE EXPOSURE									
4	Dog (NS) 4 F	51 exposures 5 days/week 6 hours/day	0.9	BW, GN, HP, BC, UR	Death				No deaths reported
					Hemato		0.9		Decreased RBC and filamented neutrophils and increased nonfilamented neutrophils
Thorium tetrafluoride									
Hall et al. 1951									

Table 2-1. Levels of Significant Exposure to Thorium – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (nCi/m^3)	Parameters monitored	Endpoint	NOAEL (nCi/m^3)	Less serious LOAEL (nCi/m^3)	Serious LOAEL (nCi/m^3)	Effect
5	Dog (NS) 2 M, 2 F	45 exposures 5 days/week 6 hours/day	1.4	BW, GN, HP, BC, UR	Death				No deaths reported
					Hemato		1.4		Decreased RBC counts
Thorium oxalate									
Hall et al. 1951									
6	Rabbit (NS) 6 M	21 exposures 5 days/week 6 hours/day	1.6	BW, GN, HP, BC, UR	Death				No deaths reported
					Hemato	1.6			
Thorium oxalate									
Hall et al. 1951									
CHRONIC EXPOSURE									
7	Rat (NS) 125 F	1 year 5 days/week 6 hours/day	0.55	BW, HP, BC, CS	Death				No deaths were observed
					Resp	0.55			
					Hemato	0.55			
					Musc/skel	0.55			
					Hepatic	0.55			
					Renal	0.55			
					Immuno	0.55			No histological alterations in lymph nodes
Thorium dioxide									
Hodge et al. 1960									

Table 2-1. Levels of Significant Exposure to Thorium – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (nCi/m^3)	Parameters monitored	Endpoint	NOAEL (nCi/m^3)	Less serious LOAEL (nCi/m^3)	Serious LOAEL (nCi/m^3)	Effect
8	Guinea pig (NS) 20 F	14 months 5 days/week 6 hours/day	0.55	BW, HP, BC, CS	Death				No deaths were observed
					Resp	0.55			
					Hemato	0.55			
					Musc/skel	0.55			
					Hepatic	0.55			
					Renal	0.55			
					Immuno	0.55			No histological alterations in lymph nodes
Thorium dioxide Hodge et al. 1960									
9	Dog (NS) 13 M, 13 F	14 months 5 days/week 6 hours/day	0.55	BW, HP, BC, CS	Death				No deaths were observed
					Resp	0.55			
					Hemato	0.55			
					Musc/skel	0.55			
					Hepatic	0.55			
					Renal	0.55			
					Immuno	0.55			No histological alterations in lymph nodes
Thorium dioxide Hodge et al. 1960									

Table 2-1. Levels of Significant Exposure to Thorium – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (nCi/m^3)	Parameters monitored	Endpoint	NOAEL (nCi/m^3)	Less serious LOAEL (nCi/m^3)	Serious LOAEL (nCi/m^3)	Effect
10	Rabbit (NS) 10 M	14 months 5 days/week 6 hours/day	0.55	BW, HP, BC, CS	Death				No deaths were observed
					Resp	0.55			
					Hemato	0.55			
					Musc/skel	0.55			
					Hepatic	0.55			
					Renal	0.55			
					Immuno	0.55			No histological alterations in lymph nodes
Thorium dioxide									
Hodge et al. 1960									

[a]The number corresponds to entries in Figure 2-2.

BC = serum (blood) chemistry; BW = body weight; CS = clinical signs; F = female(s); GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); mo = month(s); Musc/skel = muscular/skeletal; nCi = nanocuries; NOAEL = no-observed-adverse-effect level; NS = not specified; RBC = red blood cell; Resp = respiratory; UR = urinalysis

Figure 2-2. Levels of Significant Exposure to Thorium – Inhalation
Acute (≤14 days)

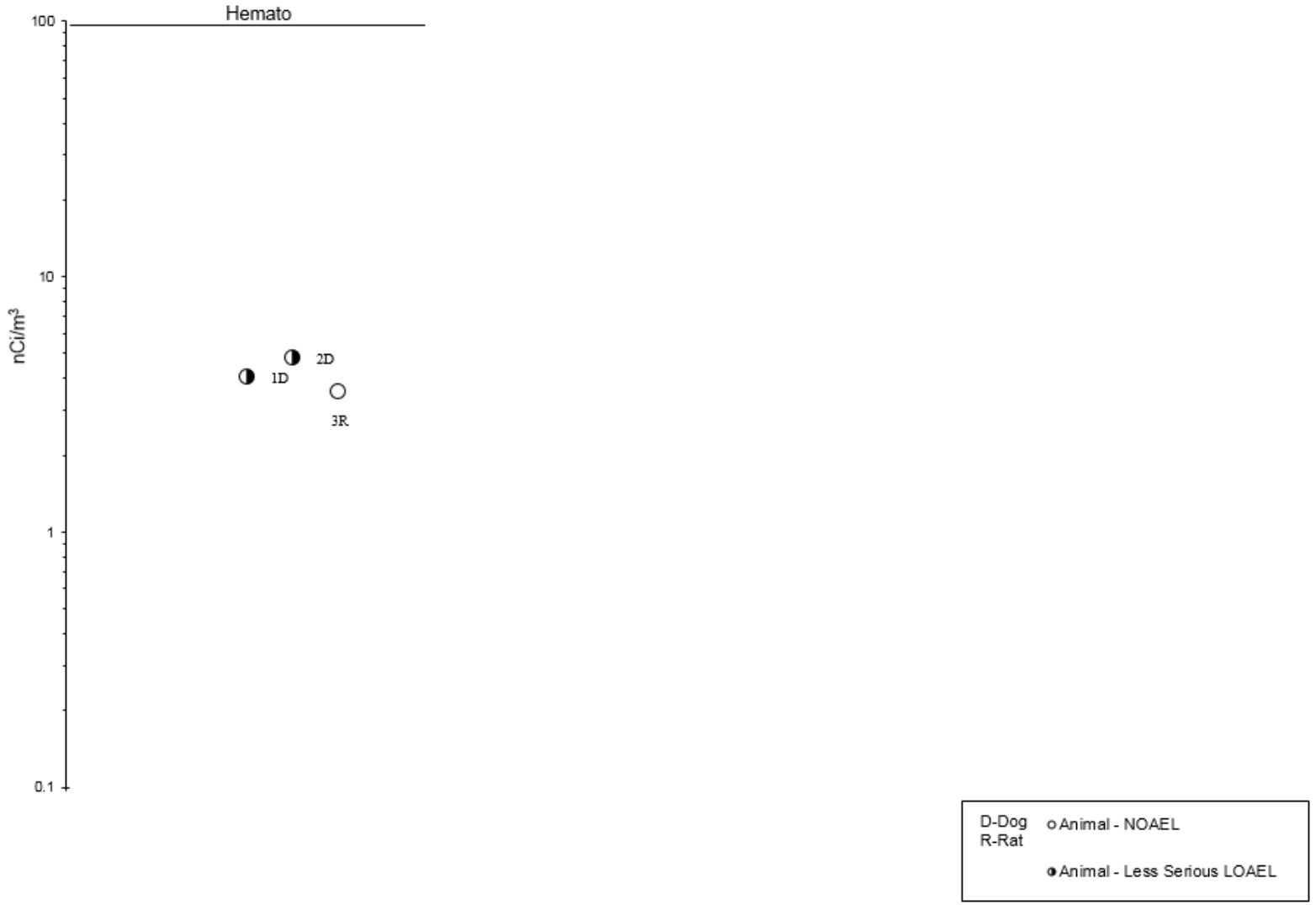


Figure 2-2. Levels of Significant Exposure to Thorium – Inhalation
Intermediate (15-364)

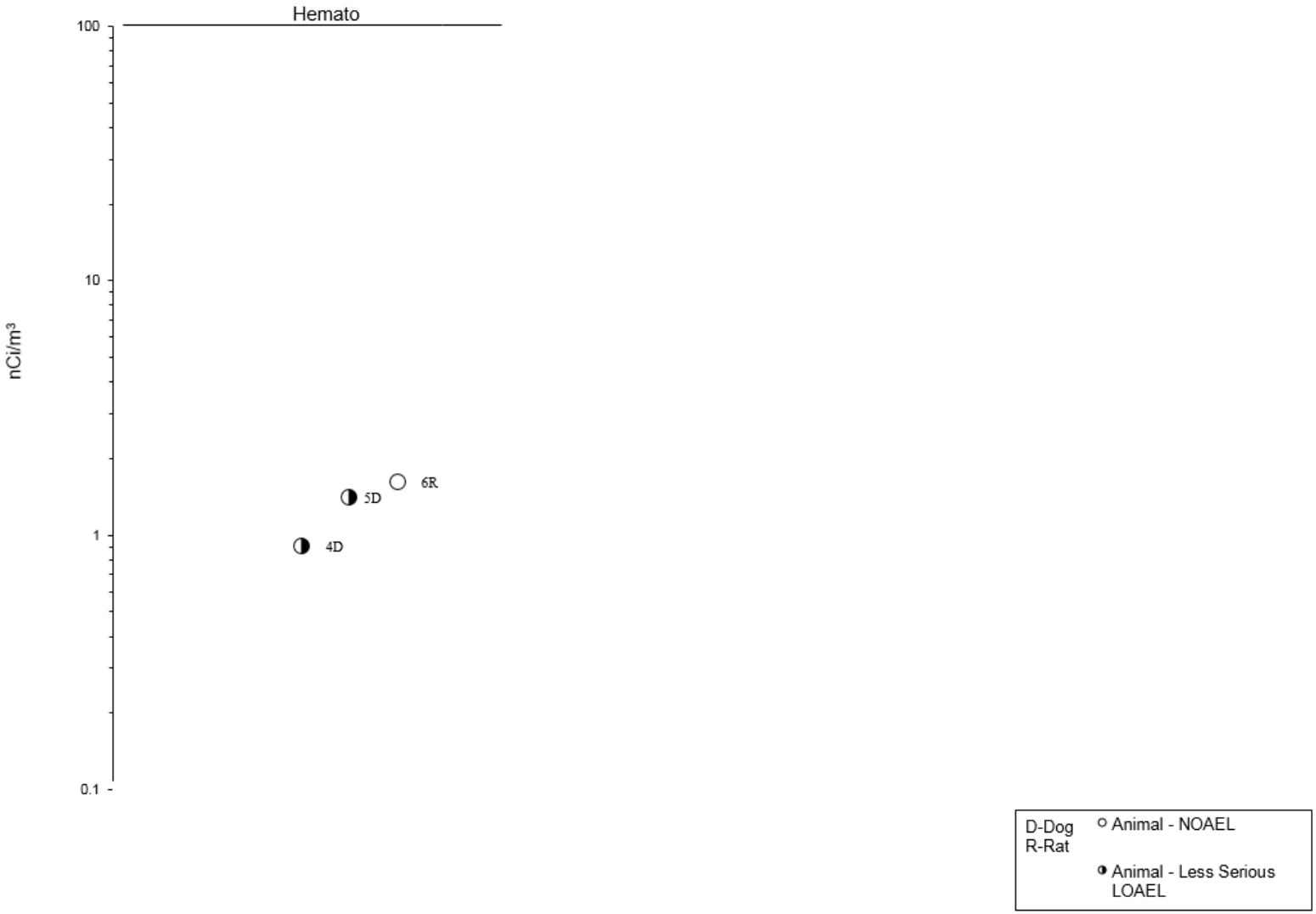


Figure 2-2. Levels of Significant Exposure to Thorium – Inhalation

Chronic (≥365 days)

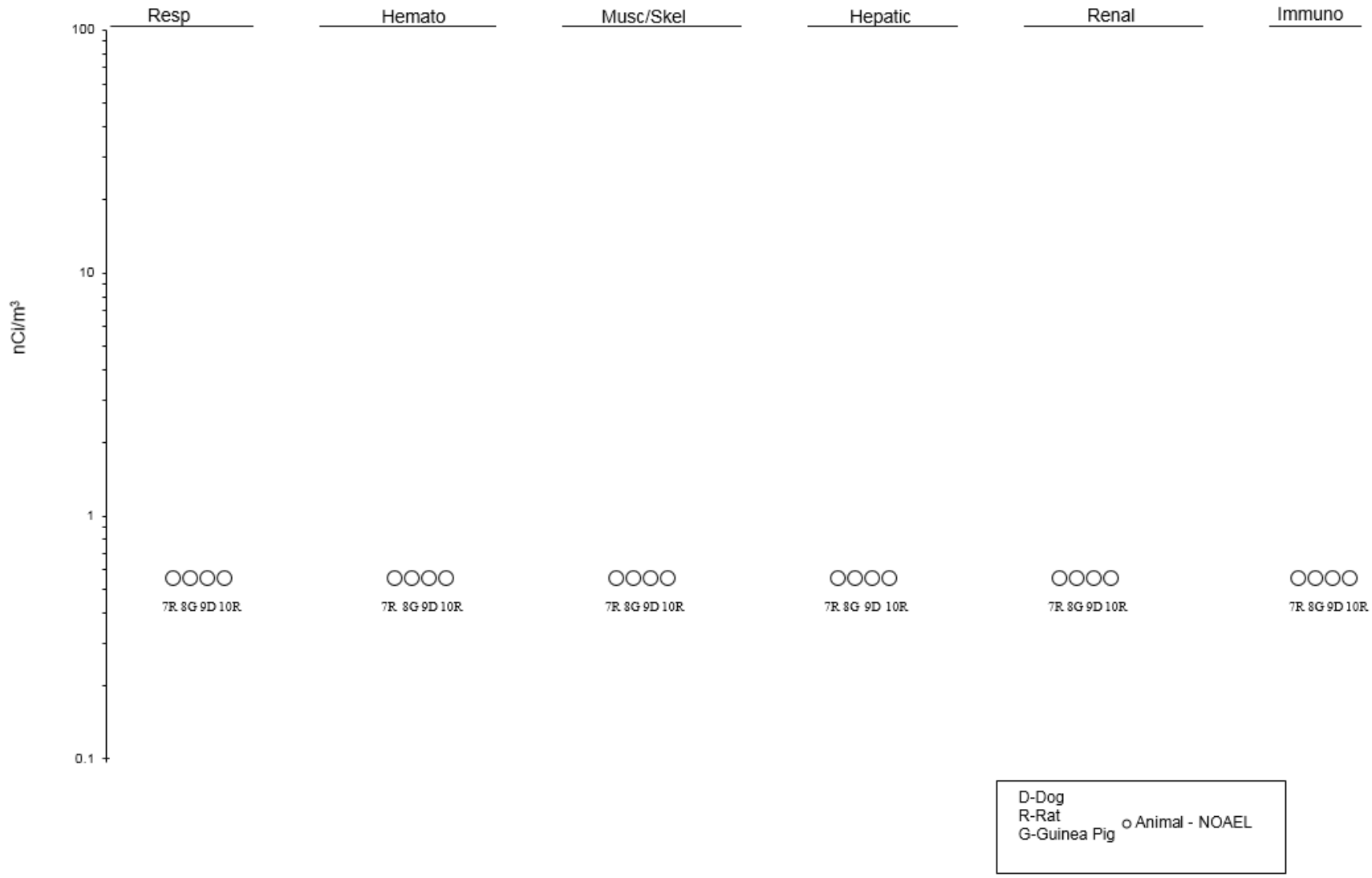


Table 2-2. Levels of Significant Exposure to Thorium – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (nCi/kg/day)	Parameters monitored	Endpoint	NOAEL (nCi/kg/day)	Less serious LOAEL (nCi/kg/day)	Serious LOAEL (nCi/kg/day)	Effect
ACUTE EXPOSURE									
1	Mouse (NS) 10–20 F	1 days (G)	84–110	GN, CS	Death	84	110		4/20 died
Thorium nitrate									
Patrick and Cross 1948									
INTERMEDIATE EXPOSURE									
2	Rat (Wistar) 20 M, 20 F	105–131 days (F)	0, 1.3, 2.1, 3.4% Th in diet; 1.3%= 130 nCi/kg/day	BW, CS, GN, HE, HP	Death				Deaths were observed at ≥2.1% dietary levels
					Bd wt			130 M	24.6% decrease in body weight gain in males
					Resp	130			
					Cardio	130			
					Gastro	130			
					Hemato	130			
					Hepatic	130			
					Renal	130			
					Repro	130			
Thorium nitrate tetrahydrate									
Downs et al. 1959									

Table 2-2. Levels of Significant Exposure to Thorium – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (nCi/kg/day)	Parameters monitored	Endpoint	NOAEL (nCi/kg/day)	Less serious LOAEL (nCi/kg/day)	Serious LOAEL (nCi/kg/day)	Effect
3	Mouse (NS) 20F	4 months (W)	12	GN, CS	Death		12		10/20 died
Thorium nitrate									
Patrick and Cross 1948									

[a]The number corresponds to entries in Figure 2-3.

Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; (F) = food; F = female(s); (G) = gavage; Gastro = gastrointestinal; GN = gross necropsy; Hemato = hematological; HP = histopathology; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Repro = reproductive; Resp = respiratory; (W) = water

Figure 2-3. Levels of Significant Exposure to Thorium – Oral
Acute (≤14 days)

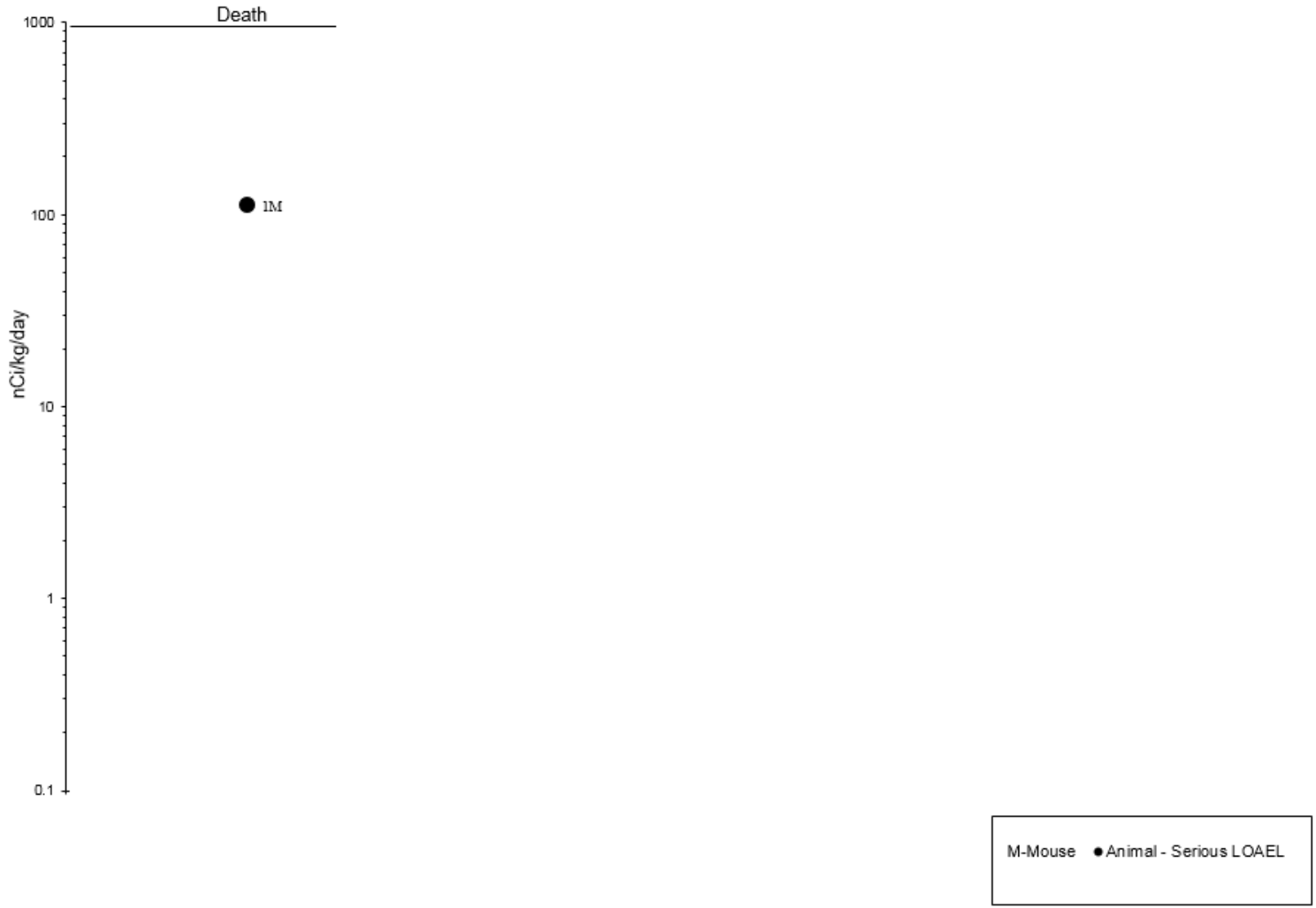


Figure 2-3. Levels of Significant Exposure to Thorium – Oral

Intermediate (15-364 days)

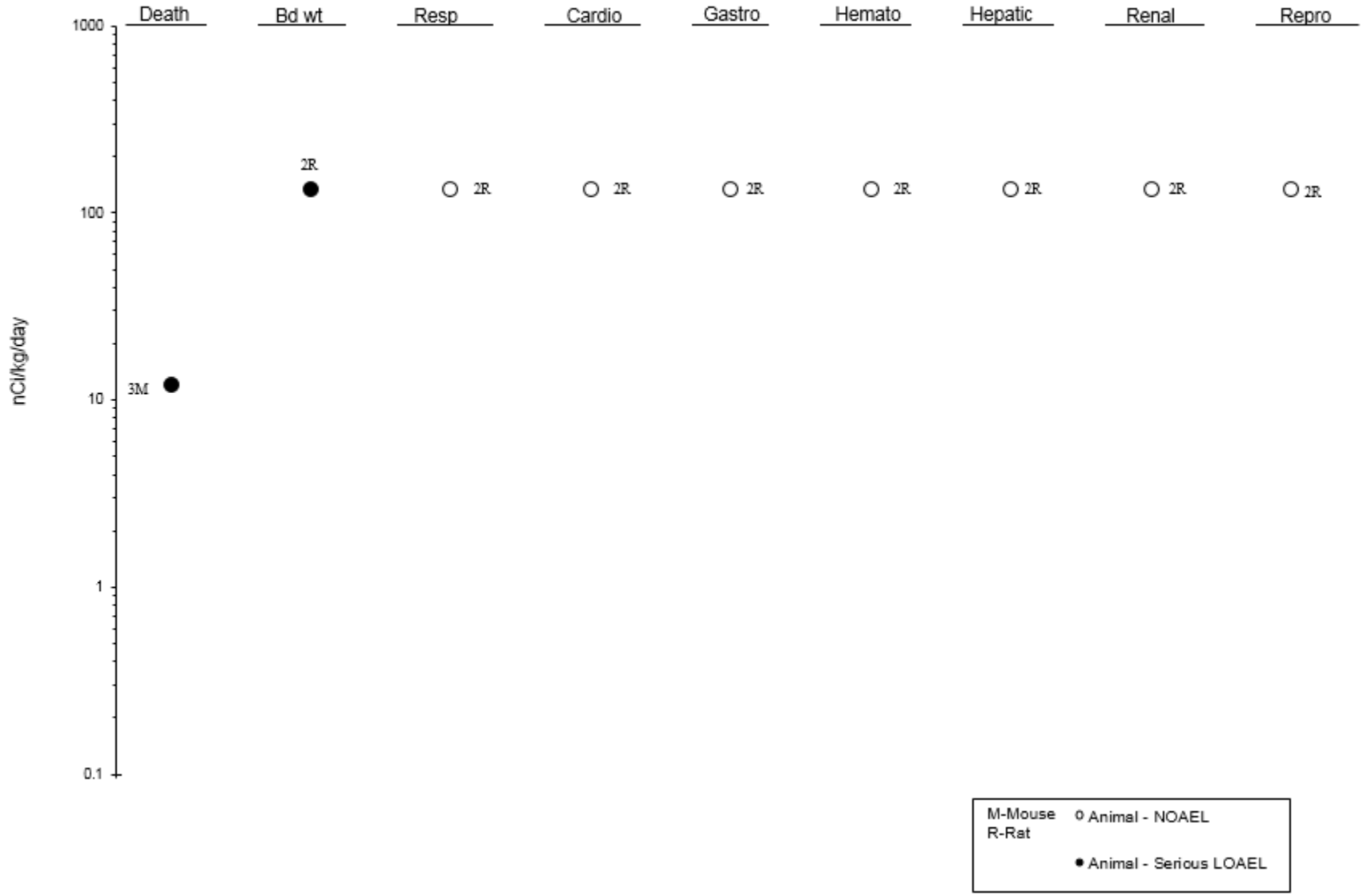


Table 2-3. Levels of Significant Exposure to Thorium – Dermal

Species (strain) No./group	Exposure parameters	Doses (nCi/kg)	Parameters monitored	Endpoint	NOAEL (nCi/kg)	Less serious LOAEL (nCi/kg)	Serious LOAEL (nCi/kg)	Effect
INTERMEDIATE EXPOSURE								
Rat (NS) 4 M	15 days	15, 29, 58	GN HP CS	Death				No deaths were observed
				Hepatic	58			
				Renal	58			
				Dermal		15		Hyperkeratinization at ≥15 nCi/kg/day; mild acanthosis at 58 nCi/kg/day
				Repro		15		Mild edema of seminiferous tubules at ≥15 nCi/kg/day; desquamation of sperm at 58 nCi/kg/day
Thorium nitrate								
Tandon et al. 1975								

CS = clinical signs; GN = gross necropsy; HP = histopathology; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Repro = reproductive

2.2 DEATH

In a study of male workers at a thorium processing facility, no increases in deaths from all causes were found; the standardized mortality ratio (SMR) was 1.05 (95% confidence interval [CI] 0.96–1.15), in comparison to U.S. white males (Polednak et al. 1983; Stehney et al. 1980); the workers were primarily employed as laborers and operators in the thorium extraction process. The estimated thorium concentrations ranged from 0.003 to 0.192 nCi/m^3 for a period of 1–33 years. In a follow-up study that also examined female workers primarily involved in the production of incandescent gas mantles, the SMRs for all causes were 1.12 (95% CI 1.05–1.21) among 3,119 male workers and 0.74 (95% CI 0.63–0.86) among 677 female workers (Liu et al. 1992).

In a series of acute- and intermediate-duration inhalation exposures to thorium nitrate, thorium dioxide, thorium fluoride, or thorium oxalate, no deaths were observed in dogs or rabbits exposed to 0.9–4.8 nCi/m^3 10–51 times (Hall et al. 1951). Similarly, no deaths were reported in rats, guinea pigs, dogs, or rabbits exposed to 0.55 nCi/m^3 as thorium dioxide for 14 months (Hodge et al. 1960). A single gavage administration of 110 nCi/kg as thorium nitrate resulted in the death of 4/20 mice (Patrick and Cross 1948); no deaths were observed at 84 nCi/kg. Repeated exposure (4 months) to thorium nitrate in drinking water resulted in 50% mortality in mice exposed to 12 nCi/kg/day (Patrick and Cross 1948). Downs et al. (1959) reported increases in mortality in weanling and mature rats exposed to dietary concentrations of thorium nitrate ≥2.1% for intermediate durations; the investigators attributed the deaths to the poor nutritional status of the rats (marked decreases in food intake and body weight gain) rather than a direct effect of thorium nitrate. With the exception of one group of animals, doses could not be calculated for this study; no deaths were observed in rats exposed to 130 nCi/kg/day. No deaths were reported in a 15-day dermal exposure rat study in which 58 nCi/kg/day as thorium nitrate was applied to the lateroabdominal and scrotal skin (Tandon et al. 1975).

Syao-Shan et al. (1970b) compared the acute lethality of thorium nitrate, thorium chloride, and thorium dioxide in mice receiving a single intraperitoneal injection. The estimated LD_{50} doses were 370.8 mg thorium/kg for thorium nitrate and 589.1 mg thorium/kg for thorium chloride; no significant increases in mortality were observed at 2,000 mg thorium/kg as thorium dioxide, which was the highest dose tested. The investigators suggested that solubility determined the relative toxicity of the three compounds. Downs et al. (1959) reported 1- and 2-day LD_{50} values of 648 and 513 mg thorium/kg, respectively, for thorium nitrate administered via intraperitoneal injection to mature female rats. When administered to

weanling rats, the LD_{50} value ranged between 852 and 1,065 mg thorium/kg, suggesting that weanlings were less sensitive than mature animals.

2.3 BODY WEIGHT

Weight loss was reported in mature rats exposed to thorium nitrate in the diet at 4.3% thorium for 90–114 days (Downs et al. 1959). However, marked decreases in food intake were also observed at this dietary concentration. In weanling rats treated with thorium nitrate in the diet for 98–137 days at concentrations ≥0.43% thorium, decreases in body weight gain were observed (Downs et al. 1959); decreases in food intake were also reported in the weanling rats. Due to inadequate reporting of food intake, doses cannot be calculated for this study, with the exception of one group for which the investigators provided dose information. A 24.6% decrease in body weight gain was observed in male rats exposed to 130 nCi/kg/day (dietary concentration of 1.3% thorium). Weight loss was also observed in rats administered a single intraperitoneal dose of 60.8 mg thorium/kg as thorium nitrate dissolved in trisodium citrate (M^{c}Clinton and Schubert 1948).

2.4 RESPIRATORY

No increase in the risk of deaths from respiratory disease (SMR 1.31, 95% CI 0.92–1.83) was observed in a study of 3,039 thorium refinery workers (Polednak et al. 1983). It is noted that the analysis did not control for smoking or exposure to other compounds, such as cerium, uranium, and other rare earth elements, which may have contributed to the overall risk. Exposure level estimates for inhalation intakes ranged from 0.003 to 0.192 nCi/m^3 for a period of 1–33 years.

In a poorly reported study, hypertrophic rhinitis and progressive pneumosclerosis (interstitial pneumonia) of the lungs were observed in rats exposed intermittently (5 hours/day, 5 days/week) for 6–9 months to an inert aerosol (loparite dust) enriched with 10 or 49% insoluble thorium dioxide, or to thorium dioxide (100%) alone (Likhachev et al. 1973a); no information on exposure levels or specific activity of the aerosol was provided. It is noted exposure to the loparite dust vehicle also resulted in lung damage, including chronic “broncho-bronchiolitis” and foci of desquamative pneumosclerosis. The investigators reported that the severity of the lung sclerosis was directly related to the radiation dose and the amount of thorium dioxide. Sclerosis 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. Since the exact amount of thorium administered was not clear from the report, the results of the study do not appear in Table 2-1.

No histopathological alterations were observed in the lungs of rats, guinea pigs, rabbits, or dogs exposed to 0.55 nCi/m^3 as thorium dioxide 6 hours/day, 5 days/week for 14 months (Hodge et al. 1960). No histological alterations were observed in the lungs of rats exposed to dietary thorium nitrate for 90–137 days at concentrations as high as 4.3% thorium (Downs et al. 1959); the lack of food consumption data precludes calculating doses for all but one group. No lung lesions were observed in the rats exposed at 1.3% thorium (130 nCi/kg/day).

Pneumonia, suppurative lesions of the bronchi with sclerotic changes of peribronchial tissue, and bronchiectasis were observed in rats receiving a single intratracheal dose of 0.192 nCi/kg of thorium dioxide (Gaidova and Syao-Shan 1970). McClinton and Schubert (1948) reported nasal hemorrhages in rats administered 60.8 mg/kg as thorium nitrate dissolved in trisodium citrate via intraperitoneal injection; the dose also resulted in lethality.

2.5 CARDIOVASCULAR

In a study of thorium process workers, no increases in deaths from circulatory diseases were found among male workers (Liu et al. 1992). However, in female workers primarily involved in the production of incandescent gas mantles, there was an inverse association between deaths from circulatory disease and thorium exposure (Liu et al. 1992). Dietary exposure to thorium (as thorium nitrate) at 130 nCi/kg/day did not result in histopathological changes in the heart of rats exposed for 105–131 days (Downs et al. 1959); no lesions were observed at higher dietary concentrations (up to 4.3% thorium).

In contrast, 11 months after a single intratracheal and intraperitoneal injection of thorium dioxide in rats, a sharp and persistent fall in blood pressure was found (Syao-Shan 1970d); however, the magnitude of the decrease in blood pressure was not dose-related.

2.6 GASTROINTESTINAL

Hall et al. (1951) reported retching, gagging, and occasional vomiting in dogs exposed to 4.0 nCi/m^3 as thorium tetranitrate 6 hours/day, 5 days/week for 10 exposures; no information on the incidence or frequency of the effect was provided. The study did not appear to use a control group, which would provide insight into whether the effect was compound specific or due to dust exposure. 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. No histopathological changes in the stomach or intestines were found in rats exposed to thorium (as thorium nitrate) for 105–131 days at 130 nCi/kg/day (Downs et al. 1959). Similarly, no gastrointestinal lesions were observed in rats exposed to higher dietary concentrations (up to 4.3% thorium) for intermediate durations; doses could not be calculated for these groups.

2.7 HEMATOLOGICAL

Information on the potential of thorium to adversely affect the hematological system comes from an occupational exposure study and several experimental animal studies. A complete blood count was done on a cohort of 273 male monazite sand refinery workers to determine the effect of thorium on the hematological system. The estimated 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 [^{220}Rn] 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 milliroetgren/hour. Because the workers were exposed to other toxic compounds (silica, yttrium, acid and alkali fumes) as well as other radioactive materials, toxic effects cannot necessarily be attributed to thorium.

A series of inhalation studies in dogs (6 hours/day, 5 days/week) reported decreases in erythrocyte counts after 10 exposures to 4.8 nCi/m^3 thorium dioxide, 45 exposures to 1.4 nCi/m^3 thorium oxalate, or 51 exposures to 0.9 nCi/m^3 thorium tetrafluoride (Hall et al. 1951). This study also found alterations in leukocytes including leukocytosis, distorted monocytes, abnormal forms of lymphocytes, and hypersegmented polymorphonuclear granulocytes in dogs exposed to 4.0 nCi/m^3 thorium nitrate; increased filamented neutrophils in dogs exposed to thorium tetrafluoride; and increased number of polymorphonuclear neutrophils in dogs exposed to thorium dioxide. No hematological alterations were observed in male and female rabbits exposed to 3.8 or 3.5 nCi/m^3 thorium dioxide, respectively, for 10–11 exposures (Hall et al. 1951). It is noted that in the Hall et al. (1951) study, no control group was used; pre-exposure blood counts were used as reference values. No effects on hematological parameters or the histopathology of the spleen were found in rats, guinea pigs, rabbits, or dogs exposed to 0.55 nCi/m^3 as thorium dioxide 6 hours/day, 5 days/week for 1 year (Hodge et al. 1960).

Dietary intake of thorium nitrate at 130 nCi/kg/day by rats treated for 105–131 days did not result in histopathological changes in the spleen or alterations in erythrocyte, leukocyte (total and differential), or platelet counts (Downs et al. 1959). Higher dietary concentrations (up to 4.3% thorium, doses could not be calculated due to lack of food consumption data) also did not result in hematological alterations in mature or weanling rats exposed for intermediate durations.

An *in vitro* study found that thorium nitrate induces aggregation and hemolysis in human erythrocytes (Kumar et al. 2010); it is not known if this would also occur *in vivo*.

2.8 MUSCULOSKELETAL

No histological alterations were observed in the femur of rats, guinea pigs, rabbits, or dogs exposed for 1 year to 0.55 nCi/m^3 as thorium dioxide for 1 year (6 hours/day, 5 days/week) (Hodge et al. 1960).

2.9 HEPATIC

The levels of aspartate aminotransferase (AST), globulin, and total bilirubin in sera of a cohort of 275 former workers in a thorium refinery were correlated with body burdens of radioactive material (Farid and Conibear 1983). The levels of AST and total bilirubin were significantly higher 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 exposure concentrations were reported.

Hepatic effects have not been observed in studies of laboratory animals. Inhalation exposure to 0.55 nCi/m^3 thorium dioxide for 1 year did not result in histopathological alterations in the livers of rats, guinea pigs, rabbits, or dogs (Hodge et al. 1960). Similarly, no histopathological changes in the liver were found in rats exposed to thorium (as thorium nitrate) in the food for 105–131 days at 1.3% (130 nCi/kg/day) or in other rats exposed at dietary concentrations as high as 4.3% thorium (Downs et al. 1959). Dermal exposure to 58 nCi/kg/day as thorium nitrate applied for 15 days to latero-abdominal and scrotal areas did not result in histopathological alterations in the liver of rats (Tandon et al. 1975).

2.10 RENAL

There are limited data on the renal toxicity of thorium in humans following inhalation, oral, or dermal exposure. In a study of former thorium refinery workers (Farid and Conibear 1983; see Section 2.9 for details), no alterations in serum albumin, total protein, or alkaline phosphatase levels were observed.

No histopathological effects on the kidneys were found in rats, guinea pigs, rabbits, or dogs exposed via inhalation to 0.55 nCi/m^3 as thorium dioxide 6 hours/day, 5 days/week for 1 year (Hodge et al. 1960) in weanling rats exposed to 130 nCi/kg/day as thorium nitrate in the diet for 105–131 days (Downs et al. 1959), weanling or mature rats exposed to dietary thorium nitrate concentrations as high as 4.3% thorium (doses could not be calculated due to lack of food intake data) for 90–137 days (Downs et al. 1959), or in rats exposed via dermal application of 58 nCi/kg/day as thorium nitrate for 15 days (Tandon et al. 1975).

2.11 DERMAL

Information on the dermal toxicity of thorium is limited to a study in which rats received daily dermal applications of thorium nitrate to the lateroabdominal and scrotal areas of rats for 15 days (Tandon et al. 1975). Mild hyperkeratinization of the lateroabdominal skin was found at ≥15 nCi/kg/day. At 58 nCi/kg/day, 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.

2.12 OCULAR

No studies examining ocular toxicity were identified in humans or animals.

2.13 ENDOCRINE

No studies examining endocrine effects were identified in humans or animals.

2.14 IMMUNOLOGICAL

Information on the immunotoxicity of thorium is limited to inhalation studies examining the lymph nodes. Progressive lymph node atrophy was observed in rats exposed to dust containing 46 or 100% thorium dioxide for 6–9 months (Likhachev et al. 1973a). A second inhalation study did not find histopathological effects in the lymph nodes of rats, guinea pigs, rabbits, or dogs exposed to 0.55 nCi/m^3

as thorium dioxide for 6 hours/day, 5 days/week for 1 year (Hodge et al. 1960); no parameters of immune function were examined.

2.15 NEUROLOGICAL

No inhalation, oral, or dermal studies evaluating neurological endpoints were identified.

A 30-day exposure to 1.09 µCi/kg/day as thorium nitrate administered via intraperitoneal injection resulted in marked edema and neuronal degeneration in the cerebellum of mice (Kumar et al. 2009). Increases in acetylcholinesterase (AChE) specific activity were observed in the cerebellum, cortex, hippocampus, and striatum regions of the brain; the increases in AChE activity were significantly correlated with increases in thorium levels in those regions of the brain. Thorium nitrate exposure also resulted in impaired learning and memory-based neurobehavior in the mice (Kumar et al. 2009).

2.16 REPRODUCTIVE

No histopathological changes in the gonads were found in male and female rats exposed for 105–131 days to 1.3% thorium as thorium nitrate in the diet (130 nCi/kg/day) (Downs et al. 1959). Dietary exposure to thorium nitrate at higher levels (up to 4.3% thorium; doses could not be calculated due to lack of food intake data) for 90–137 days did not result in histopathological changes in the gonads of mature or weanling rats (Downs et al. 1959).

Daily dermal applications of thorium nitrate to the lateroabdominal and scrotal skin of rats for 15 days resulted in mild edema of the seminiferous tubules and the interstitium at ≥15 nCi/kg/day (Tandon et al. 1975). At 58 nCi/kg/day, some desquamation of sperm and giant spermatid-type cells was found. The percentage of sperm affected by thorium treatment was not reported. Based on the rapid onset of effects, the investigators suggested that the effects were due to chemical toxicity rather than a radiological effect.

Several parenteral exposure studies examined potential testicular effects. Intratesticular injection of 1.5 mg thorium/kg as thorium nitrate resulted in decreases in testicular weight, severe testicular necrosis, which resulted in degeneration of almost all of the seminiferous tubules and a total lack of spermatozoa in rats within 2 days of injection (Kamboj and Kar 1964). Decreases in relative testes weight, deformation of seminiferous tubules with extensive degeneration of spermatogenic stages and reductions in the number of Leydig cells were observed in mice administered intraperitoneal injections of 0.5 mmol/mL/kg of thorium nitrate for 7 days (Jadon and Mathur 1983). In contrast, subcutaneous administration of

1.5 mg thorium/kg as thorium nitrate did not result in testicular alterations or alteration of residual spermatozoa in the ductus deferens in rats (Kamboj and Kar 1964) and an intravenous injection of 0.3 µCi/kg ^{238}Th (thorium compound not specified) did not result in testicular lesions in dogs (Ellis and Berlinger 1967).

2.17 DEVELOPMENTAL

No developmental toxicity studies were identified for thorium.

2.18 OTHER NONCANCER

No studies examining other noncancer endpoints were identified.

2.19 CANCER

Investigators have evaluated the carcinogenicity of thorium in two cohorts of thorium workers. The first cohort consisted of 3,039 male workers at a thorium processing facility in Illinois who began work in 1940 or later (Polednak et al. 1983; Stehney et al. 1980); most of the workers were labors and operators involved in thorium extraction. The workers were exposed to thorium and its progeny radionuclides, including ^{220}Rn (thoron). Thorium exposure was estimated using job classification and exposure duration; however, individual exposure levels were not estimated. The concentration of α-emitting radionuclides was estimated in a subset of 592 workers in various job categories; the exposure levels ranged from 0.003 to 0.192 nCi/m^3. No associations between thorium exposure and deaths from all cancers (SMR 1.21, 95% CI 0.99–1.48) or specific types of cancer were found, as compared to the mortality rates for U.S. white males. SMRs for lung cancer and pancreatic cancer were 1.44 (95% CI 0.98, 2.02) and 2.01 (95% CI 0.92, 3.82), respectively (Polednak et al. 1983). Among the subset of 592 workers with exposure to thorium dust and employment of ≥1 year, an elevated risk of death from all cancer was found (SMR 1.75, 95% CI 1.26–2.39). An association was also found for deaths from pancreatic cancer (SMR 4.13; 95% CI 1.34–9.63). The authors indicated that smoking may be a confounding factor in the increased rates of cancer; however, the smoking histories were not available for the subjects. A follow-up study of this cohort (Liu et al. 1992) was expanded to include female workers primarily working in the incandescent gas mantle area where there were low levels of thorium; the total number of examined workers was 3,796 (3,119 males and 677 females). Increases in deaths from all cancers (SMR 1.23, 95% CI 1.04–1.43) and lung cancer (SMR 1.36, 95% CI 1.02–1.78) were found among male workers; as noted for the Polednak et al. (1983) study, the study did not control for smoking,

which may have contributed to the increased risk. No increase in pancreatic cancer (SMR 1.47, 95% CI 0.70–2.71) was found. An inverse association between thorium exposure and cancer deaths were found among the female workers (all cancers SMR 0.53, 95% CI 0.36–0.78). Dividing the male workers into subgroups based on job classification, duration of employment, time since first employment, year of first employment, or age at first employment did not result in substantial variations in deaths from all cancers or lung cancer; see Table 2-4 for a summary of mortality ratios. However, it demonstrates that the increased risk was generally seen in shorter-term workers (≤1 month for lung cancer only), in workers more recently hired (<15 years since first employment), and in workers first employed at an older age (≥30 years old).

Table 2-4. Standardized Mortality Ratios for All Cancers and Lung Cancers Among Male Thorium Workers

	All cancers			Lung cancer		
	Number of deaths	SMR	95% CI	Number of deaths	SMR	95% CI
Job classification						
Laborers and operators in the thorium extraction process	113	1.23	1.01–1.47	39	1.38	0.98–1.89
Other laborers, foremen, maintenance and repair men, superintendents	19	1.44	0.86–2.24	6	1.37	0.50–2.99
Personnel in receiving, shipping, control laboratory, office, and others	21	1.28	0.79–1.96	5	1.12	0.36–2.62
Duration of employment						
≤1 month	55	1.38	1.04–1.80	22	1.80	1.13–2.73
2-12 months	44	0.99	0.72–1.33	15	1.10	0.62–1.81
≥13 months	54	1.44	1.08–1.88	13	1.16	0.62–1.99
Time since first employment						
<15 years	57	1.40	1.06–1.82	17	1.73	1.01–2.77
15–29 years	67	1.21	0.94–1.54	21	1.17	0.73–1.80
≥30 years	29	1.12	0.75–1.51	12	1.29	0.67–2.25
Year at first employment						
1915–1954	115	1.27	1.05–1.53	33	1.24	0.85–1.74
1955–1973	38	1.21	0.85–1.65	17	1.65	0.96–2.64

Table 2-4. Standardized Mortality Ratios for All Cancers and Lung Cancers Among Male Thorium Workers

	All cancers			Lung cancer		
	Number of deaths	SMR	95% CI	Number of deaths	SMR	95% CI
Age at first employment						
<20 years	7	0.85	0.34–1.75	3	1.16	0.23–3.39
20–29 years	25	0.97	0.63–1.43	7	0.81	0.33–1.67
≥30 years	121	1.38	1.15–1.65	40	1.55	1.11–2.11

CI = confidence interval; SMR = standardized mortality ratio

Source: Liu et al. 1992

The second cohort consisted of workers in the Baiyan Obo rare earth and iron mine in China. Early studies of this cohort were summarized in IARC (2001). Chen et al. (2005) noted that the ore from this mine contained 10% silicon dioxide and 0.04% thorium by weight. An elevated risk of lung cancer was found among 2,903 miners (2,390 males, 513 females) exposed to ore dust containing thorium and progeny nuclides (SMR 5.15, 95% CI 3.36–7.89). An increased lung cancer risk was also found among approximately 2,000 control miners inhaling dust free air (SMR 2.30, 95% CI 1.17–4.51). IARC (2001) notes that the ratio of the two SMRs was not significantly increased. IARC (2001) noted that the high lung cancer mortality rates in the two groups were likely due to high smoking rates (80%), as compared to the Chinese male population. A 20-year follow-up of this cohort calculated SMRs for lung cancer of 6.13 (95% CI 4.41–8.52) among the thorium dust miners and 1.90 (95% CI 0.94–3.84) in the control miners (Chen et al. 2003). The investigators (Chen et al. 2003, 2005) noted that the high cancer rate among the thorium miners was due to exposure to thorium dioxide, silica dioxide, and thoron progeny. It is noted that none of the analyses of cancer deaths adjusted for smoking or silica dioxide exposure.

The carcinogenicity of thorium has not been evaluated in laboratory animals following inhalation, oral, or dermal exposure. Parenteral studies have found increases in tumors had several sites including lungs, liver, bone, and mammary glands of rats, mice, and dogs (Bruenger et al. 1991; Dougherty et al. 1962; Gaidova and Syao-Shan 1970; Gilman and Ruckerbauer 1962; Gonzalez-Vasconcellos et al. 2011; Gossner 1982; Grampa 1967; Gridgeman 1971; Guimaraes et al. 1955; Lloyd et al. 1995; Luz et al. 1979, 1985; Mays et al. 1987; Müller et al. 1978, 1983; Spiers and Beddoe 1983; Stover 1981; Thurman et al. 1971).

The U.S. Department of Health and Human Services categorized thorium dioxide as reasonably anticipated to be a human carcinogen (NTP 2016) based on human and laboratory animal evidence of carcinogenicity following parenteral exposure to Thorotrast or colloidal thorium dioxide. IARC (2012) categorized internalized radionuclides that emit α-particles as carcinogenic to humans (Group 1). IARC (2012) also categorized ^{232}Th (as Thorotrast) as carcinogenic to humans (Group 1). IARC (2012) conclusions were based on the finding that there is sufficient evidence in humans for the carcinogenicity of ^{232}Th as stabilized ^{232}thorium dioxide in colloidal form (Thorotrast). It also considers that there is sufficient evidence in experimental animals for the carcinogenicity of ^{228}Th, ^{230}Th, and ^{232}Th. See Section 2.21 for discussion of the health effects of Thorotrast.

2.20 GENOTOXICITY

Limited information was located regarding the genotoxicity of thorium. 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), and high (0.015 nCi/kg). An increased frequency of chromosomal aberrations (dicentric ring chromosomes) was found in the 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 chromosomal aberrations. A positive correlation was not established between the frequency of chromosomal aberrations and duration of employment. 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. Based on the limited human data, thorium appears to be a genotoxic agent.

A mixture of thorium and lanthanum in the ratio found in Brazilian monazite sand was evaluated *in vitro* for cytotoxicity and genotoxicity to human T-lymphocyte leukemia cells. The mixture was found to be cytotoxic, but not genotoxic (Oliveira et al. 2014).

A study by Nishioka (1975) screened thorium chloride (0.05 M) as a potential mutagen by determining whether it inhibited bacterial growth in *Bacillus subtilis* strains H17 (Rec$^+$, *arg*$^-$, and *trp*$^-$) and M45 (Rec$^-$, *arg*$^-$, and *trp*$^-$). 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 oxvtoca* or *Klebsiella pneumoniae* (Wong 1988).

Refer to Section 2.21 for information regarding the genotoxicity of Thorotrast.

2.21 THOROTRAST

Thorotrast (a colloidal solution of thorium dioxide [$^{232}ThO_2$]) is an α-particle emitting contrast medium that was injected intravascularly into patients (estimates in the millions) throughout the world (mostly in the 1930s and 1940s), particularly to visualize vascular structures. However, thorium became sequestered mainly in the reticuloendothelial system (mostly liver, spleen, and red bone marrow) where thorium and its progeny caused a variety of adverse health effects.

Distribution, Retention, and Dosimetry of Thorotrast. Approximately 97% of intravenously-injected Thorotrast is taken up by the reticuloendothelial system (RES) and distributed to the liver (59%), 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 ^{228}Ra and ^{224}Ra, produced by decay of their parent nuclides, escapes from Thorotrast deposits 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).

Estimated average dose rates from the intravenous injection of 30 mL of Thorotrast were 30 rad/year in liver, 80 rad/year in spleen, 10 rad/year in red bone marrow, 4.5 rad/year in lungs, and 15 rad/year in the cells on the bone surface. The dose to compact bone was 3.3 rad/year and the dose to cancellous bone was 4.8 rad/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 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 μm of bone surfaces) to be about 16 rad/year (7 rad/year from ^{224}Ra [5.1], ^{228}Th [1.5], and ^{228}Ra [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 doses 30 years after injection of 25 mL of Thorotrast would be 750 rad in liver, 2,100 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.

The distribution of Thorotrast-derived thorium activity in organs from a female subject who had been injected with Thorotrast 36 years earlier was evaluated using autopsy tissues from the U.S. Transuranium and Uranium Registry (Kathren and Hill 1992; McInroy et al. 1992; Priest et al. 1992). More than 90% of the thorium was found in the RES, which includes liver (approximately 44–47% of the total), skeleton (32–35%), spleen (11–13%), and lymph nodes (0.28–0.65%). Radiation absorbed doses to the female subject were estimated to have been 121 Gy (12,100 rad) in the spleen (resulting in hyposplenism), 15 Gy (1,500 rad) in the liver, 4 Gy (400 rad) in the skeleton, and 16 Gy (1,600 rad) in the injection site granuloma or Thorotrastoma (Kathren and Hill 1992; McInroy et al. 1992).

Priest et al. (1992) reported that Thorotrast does not distribute uniformly in liver and bone. ^{232}Th radioactivity in bone marrow was largely restricted to areas of cellular bone marrow where it was found throughout the red marrow tissue and concentrated within cells that were commonly aggregated within focalized areas of the marrow. Total bone concentrations of ^{232}Th from highest to lowest were in the pelvis and vertebrae, ribs, upper leg, shoulder and skull, and other extremities. However, disequilibrium in the ^{228}Th:^{230}Th ratio demonstrates some mobility of the more soluble ^{228}Ra intermediary isotope, allowing the ^{228}Th progeny to deposit on distal bone surfaces, such as the fibula that has little red marrow. This is consistent with thorium being a bone surface seeker (Lloyd et al. 1984), while colloidal Thorotrast enters the marrow cavities. Significant deposits were not found in fatty yellow marrow (Kathren and Hill 1992).

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; Riedel et al. 1979). Riedel et al. (1979) evaluated the distribution of injected thorium dioxide colloids (Thorotrast) in rats, mice, and a single dog, and compared distribution patterns with results obtained for mice, rabbits, and humans by other investigators. Of the injected Thorotrast dose, the liver accounted for 37–75% (rat), 51.8 and 57.8% (mouse), 54.1% (rabbit), 66.2% (dog), and 59% (human). The spleen accounted for 3.5–15.9% (rat), 18.8–18.9% (mouse), 3.2% (rabbit), 4.1% (dog), and 26.5% (human). The study concluded that the biological behavior of colloids was generally similar in humans and animals.

Humphreys et al. (1998) injected four monkeys with Thorotrast to assess any inhomogeneities in bone marrow distribution. Thorotrast was found to evenly distribute in the red marrow at 1 week post-injection. However, Priest et al. (1992) found that after 3–4 years, Thorotrast was deposited as conglomerates within macrophages, similar to the aggregations observed in the red bone marrow of the human autopsy case.

The biological half-time for Thorotrast is estimated to be >400 years, based on measuring thorium and progeny in excreta from Thorotrast patients, determining that <1% of the thorium was excreted during the early period following injection, and analyses of thorium in their autopsy tissues (Hursh et al. 1957). Therefore, most intravascularly-injected Thorotrast was retained in the RES for a lifetime once it was deposited in tissue; those atoms that decayed and became more soluble progeny could redistribute, but very little of the thorium itself was excreted.

Toxic Effects of Thorotrast. The health effects of Thorotrast has been studied for many decades following its use as a contrast medium in patients worldwide. Table 2-5 summarizes selected results from recent follow up studies of intravascularly-injected Thorotrast cohorts in Germany (Becker et al. 2008), Portugal (dos Santos Silva et al. 2003), Denmark and Sweden (Travis et al. 2003), the United States (Travis et al. 2003), and Japan (Mori et al. 1999b). Common to these follow up studies was extremely high rates of liver cancer. Other commonly-reported effects associated with Thorotrast included nonneoplastic liver disease, blood disorders, hematopoietic cancers, and cancer of the bile duct and gall bladder.

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).

Table 2-5. Selected Thorotrast Treatment-Related Health Effects in Humans

Becker et al. 2008 (Germany)

Study design: Cohort study of 2,326 Thorotrast-injected patients and 1,890 unexposed control patients from the same hospitals in West Germany and Vienna, Austria. Study groups were identified in 1967 with follow up through 2004 (9 Thorotrast-injected patients and 151 control patients still alive). SMRs (reference=100) were calculated for Thorotrast-injected subjects and control subjects using mortality rates of West Germany from 1952 to 2002 as reference. RRs were calculated as the ratio between SMR for Thorotrast-injected subjects and SMR for unexposed control subjects.

Results: Thorotrast treatment was positively associated with death from multiple causes, particularly malignancies of the liver and hematopoietic system; life expectancy was shortened by 14 years; and mortality was increased with cumulative time since first exposure.

Cause of death	Thorotrast-exposed SMR (95% CI)	Unexposed SMR (95% CI)	Exposed/unexposed RR (95% CI)
Males			
Total mortality	287 (273–301)	153 (145–162)	1.9 (1.7–2.0)
Diseases of nervous system, eye, ear	1,169 (956–1,430)	493 (380–641)	2.4 (1.7–3.4)
Diseases of the circulatory system	150 (135–166)	104 (95–115)	1.4 (1.2–1.7)
Diseases of the digestive system	641 (568–724)	127 (99–163)	5.0 (3.8–6.8)
Neoplasms (benign/unknown characteristics)	1,116 (873–1,426)	300 (198–456)	3.7 (2.3–6.4)
Malignant neoplasms	398 (366–433)	109 (95–125)	3.7 (3.1–2.0)
Digestive organs and peritoneum	616 (554–687)	116 (94–143)	5.3 (4.2–6.8)
Liver and intrahepatic bile ducts	16,695 (14,703–18,957)	238 (107–529)	71 (32–195)
Gall bladder and extrahepatic bile ducts	1,656 (1,183–2,318)	200 (90–446)	8.1 (3.4–23.6)
Pancreas	288 (174–478)	53 (19.9–141)	5.5 1.7–22.7)
Male genital organs	269 (187–387)	119 (82–173)	2.2 (1.3–3.8)
Brain, unspecified parts of nervous system	933 (595–1,463)	296 (141–620)	3.3 (1.3–9.2)
Multiple myeloma, immunoproliferative	464 (208–1,032)	50 (7–352)	9.2 (1.1–425)
Myeloid leukemia	675 (374–1,219)	89 (22–357)	7.6 (1.7–70)
Leukemia (unspecified cell type)	1,330 (802–2,207)	129 (32–517)	10.2 (2.4–92)

Table 2-5. Selected Thorotrast Treatment-Related Health Effects in Humans

Females			
Total mortality	387 (357–419)	212 (192–233)	1.8 (1.6-2.1)
Diseases of the digestive system	784 (623–986)	229 (153–341)	3.4 (2.1–5.7)
Neoplasms (benign/unknown characteristics)	2,579 (1,971-3376)	281 (126–626)	8.8 (3.8–25)
Malignant neoplasms	395 (339–460)	174 (140–217)	2.3 (1.7–3.0)
Digestive organs and peritoneum	480 (382–601)	136 (92–201)	3.5 (2.2–5.8)
Liver and intrahepatic bile ducts	12,680 (9,337–17,221)	439 (110–1,753)	34 (8.9–292)
Brain, unspecified parts of nervous system	3,320 2,064–5,340)	185 (26–1,312)	17.0 (2.7–711)

dos Santos Silva et al. 2003 (Portugal)

Study design: Cohort study of 1,096 Thorotrast-injected patients and 1,014 nonradioactive contrast-injected patients (controls) from hospitals in Portugal. Study groups were identified in 1961 with follow up through 1996. SMRs (reference=1) were calculated for Thorotrast-injected subjects and control subjects using national mortality rates for Portugal for the years 1930 to 1996 as reference. RRs were calculated as the ratio between SMR for Thorotrast-injected subjects and SMR for unexposed control subjects.

Results: Thorotrast treatment was positively associated with death from multiple causes, particularly chronic liver disease, liver cancer, neoplastic and nonneoplastic hematological disorders, and nonneoplastic diseases of the respiratory system; risks for these conditions remained high for >40 years following Thorotrast treatment.

Cause of death	Thorotrast-exposed SMR	Unexposed SMR	Exposed/unexposed RR (95% CI)
All causes	3.26[a]	1.24[a]	2.63 (2.28–3.04)
All malignant and benign neoplasms	7.02[a]	1.04	6.72 (4.83–9.51)
Hematological diseases	21.7[a]	3.62	6.00 (1.14–59.2)
Diseases of nervous system	16.8[a]	1.33	12.7 (3.89–65.2)
Diseases of the respiratory system	2.42[a]	0.56	4.31 (2.15–9.22)
Chronic liver disease	5.74[a]	1.12	5.12 (2.62–10.7)
Other diseases of the digestive system	4.33[a]	0.89	12.0 (2.75–108)
Neoplastic/nonneoplastic hematological diseases	11.6[a]	1.02	11.4 (3.36–60.2)
Cancer of lymphatic and hematopoietic tissues	9.17[a]	0.42	21.9 (3.24–935)
Leukemia	8.17[a]	0.80	10.2 (1.24–471)
Liver cancer	338[a]	7.98[b]	42.4 (13.90–210)
Liver cancer and chronic liver disease	15.2[a]	1.35	11.2 (6.49–20.7)
All Thorotrast-related causes	6.88[a]	1.08	6.35 (4.75–8.59)

Table 2-5. Selected Thorotrast Treatment-Related Health Effects in Humans

Travis et al. 2003 (Denmark and Sweden)

Study design: Cohort study of 773 and 431 Thorotrast-injected patients in Denmark and Sweden, respectively, and 1,180 nonradioactive contrast-injected patients (controls) in Denmark. Thorotrast treatment was undertaken during 1935–1947 in Denmark and 1932–1950 in Sweden. Registry-based patient follow up began 2 years after angiography and continued until January 20, 1992 in Denmark and December 31, 1992 in Sweden. For site-specific cancer incidence, SIRs (reference=1) were calculated as the ratio of observed to expected cases in the general population. RRs were calculated as the ratio between the SIR for Thorotrast-injected subjects and the SIR for unexposed control subjects.

Results: Thorotrast treatment was positively associated with all cancers and selected site-specific cancer, particularly cancer of the liver, bile duct, and gall bladder, and leukemia. Risk of cancer increased with time since Thorotrast treatment and persisted for 50 years. Increasing cumulative radiation dose was associated with increasing risk of cancer.

Cancer cause of death	Thorotrast-exposed SIR	Unexposed SIR	Exposed/unexposed RR (95% CI)
All cancers	3.3[b]	1.0	3.4 (2.9–4.1)
All cancer except brain and nervous system	3.2[b]	1.0	3.5 (2.9–4.2)
Stomach	1.2	0.5	2.7 (1.1–7.9)
Liver (primary)	108.9[b]	0 (1.5 expected)	Infinity (44.2–infinity)
Liver (not specified as primary)	33.0[b]	0 (1.0 expected)	Infinity (8.2–infinity)
Bile ducts	17.1[b]	0.6	26.4 (4.3–1,133.9)
Gall bladder	9.9[b]	1.1	11.0 (1.3–391.0)
Pancreas	2.0	0.8	3.8 (1.3–12.3)
Ovary, fallopian tube, broad ligament	2.0	0.5	4.3 (1.1–24.3)
All male genital	1.5	0.5	4.7 (1.8–15)
Prostate	1.4	0.5	4.5 (1.6–16.3)
Kidney	2.7[b]	0.8	5.7 (1.9–21.0)
Metastases	8.3[b]	0.4	12.2 (3.3-989.7)
Leukemia, all non-chronic lymphocytic leukemia	15.2[b]	0.9	15.2 (4.4–149.6)
Thorotrast-related cancers	37.5[b]	0.6	76.2 (32.2-247.8)

Table 2-5. Selected Thorotrast Treatment-Related Health Effects in Humans

Travis et al. 2003 (United States)

Study design: Cohort study of 446 Thorotrast-injected patients and 212 nonradioactive contrast-injected patients (controls) in the United States. Thorotrast treatment was undertaken during 1935–1955. Registry-based patient follow-up began 2 years after angiography and continued until December 31, 1992. For site-specific cancer mortality, SMRs (reference=1) were calculated as the ratio of observed to expected cases in the general population. RRs were calculated as the ratio between the SMR for Thorotrast-injected subjects and the SMR for unexposed control subjects.

Results: Thorotrast treatment was positively associated with all cancers and particularly with liver cancer.

Cancer cause of death	Thorotrast-exposed SIR	Unexposed SIR	Exposed/unexposed RR (95% CI)
All cancers	3.8[b]	1.4	4.0 (2.5–6.7)
All cancer except brain and nervous system	3.1[b]	1.0	5.3 (3.1–9.7)
All digestive organs and peritoneum	3.4[b]	0.8	8.9 (3.0–38.1)
Liver	25.1[b]	2.2	22.5(1.8–464.3)
Thorotrast-related cancers	15.3[b]	1.8	20.1 (2.2–73.4)

Table 2-5. Selected Thorotrast Treatment-Related Health Effects in Humans

Mori et al. 1999b (Japan)

Study design: Cohort study of 412 Thorotrast-injected war-wounded veterans and 1,649 war-wounded veterans not injected with Thorotrast (controls) in Japan. For 262 Thorotrast-injected patients, follow-up was initiated at the time of injection; for the other 150 Thorotrast-injected patients, follow-up began January 1, 1979. Follow-up of controls was initiated on the date of injury. Follow-up was terminated on July 15, 1998. Registry-based patient follow up began 2 years after angiography and continued until December 31, 1992. Rate ratios were calculated for major causes of death.

Results: Thorotrast treatment was positively associated with several causes of death, particularly for liver cancer, leukemia, and liver cirrhosis. Rate ratios for all deaths of Thorotrast patients began to increase after a 20-year latent period.

Cause of death	Rate ratio (95% CI)
All causes	2.5 (2.2–2.8)
Liver cancer	35.9 (24.2–53.4
Liver cirrhosis	6.9 (4.0–12.0)
Lung cancer	2.0 (1.0–3.9)
Leukemia	12.5 (4.5–34.7)

[a]p<0.001
[b]p<0.05

CI = confidence interval; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio

Genotoxicity of Thorotrast. 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).

Kyoizumi et al. (1992) and Umeki et al. (1991) reported significantly increased frequencies of mutant T lymphocytes defective in T-cell receptor gene expression in the peripheral blood of patients injected with Thorotrast or ^{131}I, but not in atomic bomb survivors in Japan. The authors suggested that mutation frequency might be used as a radiation dosimeter to identify individuals who recently had been exposed to high doses of radiation, and noted that the analysis required only 1 mL of blood, commercially-available antibodies, and equipment available in many laboratories.

Radiation-induced increased frequencies of chromosomal aberrations (multicentrics and centric and acentric rings), but not mutations, have been reported in peripheral blood lymphocytes at the hypoxanthine phosphoribosyltransferase locus (Littlefield et al. 1997; Platz et al. 2000) or in bone marrow hemopoietic stem cells (Tanosaki et al. 1999) of Thorotrast patients.

Andersson et al. (1995b) evaluated the potential for alpha radiation to increase the rate of p53 point mutations in Thorotrast patients. Tissues containing 18 hepatocellular carcinomas, 9 cholangio-carcinomas, and 9 hepatic angiosarcomas were evaluated, with attention being paid to codon 249 of the p53 gene. No high scores were observed for p53 protein expression, and the scores appeared to be lower than those reported for European hepatocellular carcinomas.