Table 2.10. Cohort studies of exposure to thorium-232 and its decay products

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Travis *et al*. (2003) Denmark & Sweden Thorotrast patients	International cohort of patients injected during cerebral angiography during 1935-1963 with either Thorotrast (1204 patients, 44.4% female) or a similar but non-radioactive agent (1180 patients, 52.6% female) and who survived 2 or more years. Dose-response analyses based on 949 patients for whom the administered amount of Thorotrast was known and who did not have Thorotrastomas recorded. Cancer incidence follow-up began 2 years after arteriography, or at the time of establishment of the cancer registry in Denmark (1 January 1943) and Sweden (1 January 1958) if this were later. Follow-up ended on the earliest of date of death or emigration, or 20 January 1992 in Denmark and 31 December 1993 in Sweden. Case ascertainment in the Danish and Swedish Cancer Registries is estimated to be more than 95% complete.	Use of a surrogate measure that took into account the volume of Thorotrast administered and time since administration, ie. [ml of Thorotrast injected x max {0, years since injection - 5}].		*Surrogate for cumulative dose (ml-years, x 100)*			Country, age, gender, calendar period	Statistically significant trends in incidence with cumulative dose surrogate also seen for gallbladder, pancreatic, peritoneum and other digestive cancers. Relative to unexposed patients, Thorotrast patients had statistically significantly raised risks for cancers of the stomach (RR 2.7), liver (RR Inf), bile ducts (RR 26.4), gallbladder (RR 11.0), ovary, tube, and broad ligament (RR 4.3), prostate (RR 4.5), kidney (RR 5.7), brain and other nervous system (RR 2.5), metastases (RR 12.2), and non-CLL leukaemia (RR 15.2), plus all cancers (RR 3.4). Thorotrast-exposed patients experienced increased risks of cancer throughout life, with a cumulative risk of 97% at 50 years of follow-up for those who received more than 20 ml.
			All cancers	0–29	122	2.5 (1.9, 3.2)		
				30–49	105	3.1 (2.4, 3.9)		
				50–69	78	5.5 (4.2, 7.2)		
				70+	70	7.6 (5.7, 10.0)		
						Test for linear trend: P<0.001		
			Liver, primary	0–29	10	Inf (9.8, Inf)		
				30–49	30	Inf (40.8, Inf)		
				50–69	36	Inf (123.9, Inf)		
				70+	34	Inf (169.8, Inf)		
						Test for linear trend: P<0.001		
			Non-CLL leukaemia	0–29	11	16.1 (3.9, 165.5)		
				30–49	9	28.1 (5.7, 263.8)		
				50–69	2	11.5 (1.2, 219.1)		
				70+	2	25.1 (1.7, 331.7)		
						Test for linear trend: P=0.31		
			Pancreas	Overall	11	3.8 (1.3, 12.3)		
				0–29	1	1.4 (0.0, 6.1)		
				30–49	0	0.0 (0.0, 6.1)		
				50–69	3	9.6 (1.3, 43.7)		
				70+	2	8.5 (0.8, 52.2)		
						Test for linear trend: P=0.05		

Table 2.10. Cohort studies of exposure to thorium-232 and its decay products

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Travis *et al*. (2003) United States Thorotrast patients	Cohort of patients injected during cerebral angiography in 1935–1963 with either Thorotrast (446 patients, 48.4% female) or a similar but non-radioactive agent (212 patients, 48.1% female) and who survived 2 or more years. Dose-response analyses based on 379 patients for whom the administered amount of Thorotrast was known and who did not have Thorotrastomas recorded. Mortality follow-up to 31 December 1992. 6% of patients were lost to follow-up. Cause of death was available for 98.0% of deceased patients.	Use of a surrogate measure that took into account the volume of Thorotrast administered and time since administration, ie. [ml of Thorotrast injected x max {0, years since injection - 5}].		*Surrogate for cumulative dose (ml-years, x 100)*			Age, gender, calendar period	Relative to unexposed patients, Thorotrast patients had statistically significantly raised risks for mortality from all cancer (RR 4.0, 95% CI: 2.5–6.7), with similar excesses in males and females, as well as for cancers of the liver (RR 22.5), digestive organs and peritoneum (RR 8.9), and lymphopoietic sites (RR 9.8). Relative to national rates, statistically significant excesses were also seen observed for mortality from cancers of buccal cavity and pharynx (SMR 5.9) and bone (SMR 13.9). The relative risk of death increased with since Thorotrast exposure for all cancers, cancers of the digestive organs and peritoneum, liver (*P* trend < 0.001 in each case), lung (*P* trend=0.039) and all lymphopoietic cancers, due primarily to leukaemia (*P* trend=0.02).
			All cancers	0–29 30–49 50–69 70+ *Test for linear trend: P=0.009*	29 15 12 36	1.9 (1.1, 3.2) 2.9 (1.4, 5.6) 3.4 (1.6, 7.0) 7.0 (3.9, 12.9)		
			Liver	0–29 30–49 50–69 70+ *Test for linear trend: P=0.06*	1 2 4 14	7.0 (0.0, 115.6) 11.3 (0.4, 495.9) 30.5 (3.1, 1526.7) 40.6 (13.3, 3700)		
			All lymphopoietic cancers	0–29 30–49 50–69 70+ *Test for linear trend: P=0.90*	4 2 2 3	6.8 (0.4, 16.8) 5.0 (0.2, 22.2) 5.0 (0.3, 35.6) 5.4 (0.6, 33.2)		
dos Santos Silva *et al*. (2003) Portugal Thorotrast patients	Cohort of 1024 systemically exposed Thorotrast patients, 1014 unexposed patients and 240 locally exposed patients. Thorotrast was administered in 1929-1959, mainly for cerebral angiography in the case of systemic exposure and entirely for visualization of the perinasal sinus in the case of local	Use of a surrogate measure that took into account the volume of Thorotrast administered and time since administration, ie. [ml of Thorotrast injected x max {0,		*Surrogate for cumulative dose (ml-years)*	*Systemically exposed patients*	**SMR**	Age, calendar period, gender	Relative to unexposed patients, there were increased risks for cancers of the brain (RR 2.94), bone (RR 7.60), lung (RR 9.07) and female breast (RR 1.93) among systemically exposed patients, based on 10, 5, 4 and 3 deaths respectively, but none of
			All malignant and benign neoplasms	0–99 100–199 200–399 400–599 600+ *Test for linear*	11 10 23 31 64	7.59 (3.79, 13.6) 5.31 (2.55, 9.76) 4.79 (3.04, 7.19) 7.25 (4.92, 10.3) 8.34 (6.45, 10.6)		

Table 2.10. Cohort studies of exposure to thorium-232 and its decay products

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
	exposure. Cohort contains only persons who were successfully traced and represent 59% of the systemically exposed patients, 48% of the locally exposed patients, and 46% of the unexposed patients initially identified from hospital records. Mortality follow-up to end of 1996. Death certificates found for 80-85% of known deaths.	years since injection - 5}]. No account taken of preferential deposition of Thorotrast in certain organs of the body, the self-absorption of alpha particles within Thorotrast conglomerates or the impact of tissue necrosis and regeneration.				*trend: P=0.09*		these was statistically significant. Among locally exposed patients, there were no statistically significant excesses in mortality from oropharyngeal or nasal cancers, or from any other cause.
			Benign and malignant haematological diseases (ICD9: 204–208, 280–289)	0–99 100–199 200–399 400–599 600+	1 2 5 0 8	6.33 (0.16, 35.3) 12.42 (1.50, 44.9) 14.49 (4.71, 33.8) 0 (0, 13.5) 15.78 (6.81-31.1) *Test for linear trend: P=0.57*		
			Non-CLL leukaemia (ICD9: 204-208)	Overall	6	10.2 (1.24, 471)		
			Liver cancer and chronic liver diseases (ICD9: 155.0, 571)	0–99 100–199 200–399 400–599 600+	0 1 11 22 60	0 (0.00, 5.96) 1.42 (0.04, 7.89) 6.76 (3.38, 12.1) 17.31 (10.9, 26.2) 31.61 (24.1-40.7) *Test for linear trend: P<0.001*		
Becker et al. (2008) Germany Thorotrast patients (mortality)	Cohort of 2326 patients examined with Thorotrast for cerebral angiography (about 70%) or arteriography of the upper and lower limbs (about 30%), identified from records of 31 hospitals in the former West Germany and Vienna (Austria). Comparison group of 1890 subjects was selected from patients of the same hospitals. Active mortality follow-up to the end of 2004; 0.2% lost to follow-up. Cause-of-death identified from family physicians, hospitals, post-mortems; death certificates available for 90% of deceased cohort members.	Analyses by time since first exposure; measures of radiation dose not considered here.	All malignant neoplasms (ICD9: 140-208)	<u>Males</u> Overall *Time since first exposure (years)* <10 10–19 20–29 30+ <u>Females</u> Overall *Time since first exposure (years)* <10 10–19 20–29 30+ <u>Males</u> Overall *Time since first exposure (years)*	542 27 41 133 341 165 15 23 34 93 238 	3.7 (3.1–4.3) 1.6 (0.8–2.9) 1.2 (0.7–1.9) 2.2 (1.6–3.2) 7.7 (6.1–9.6) 2.3 (1.7–3.0) 1.7 (0.7–4.2) 0.8 (0.5–1.5) 1.0 (0.6–1.8) 7.0 (4.4–11.7) 71 (32–195) 2.0 (0.1–118)	Age, calendar period	Statistically significantly raised risks seen among Thorotrast patients relative to the control group for cancers of: liver, gallbladder and extrahepatic bile ducts, pancreas, prostate, brain, unspecified sites and haematopoietic malignancies (males); and liver, brain and unspecified sites (females). An earlier analysis of the German cohort by van Kaick et al. (1999) reported associations between the amount of Thorotrast injected and each of liver cancer, cancers of the gallbladder and

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Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
			Liver and intrahepatic bile ducts (ICD9: 155)	<10 10–19 20–29 30+	2 5 55 176	- 13.8 (4.5–69) 249 (68–2075)		extrahepatic lung ducts, and haematopoietic malignancies.
				<u>Females</u> Overall *Time since first exposure (years)* <10 10–19 20–29 30+	 41 0 0 7 34	34 (8.9–292) - - - 		
Mori *et al.* (1999b) Japan Thorotrast patients	Cohort of 412 war-wounded veterans injected with Thorotrast, based on two groups of patients, together with a cohort of 1649 war-wounded veterans who were not injected with Thorotrast. Mortality follow-up from the date of Thorotrast injection for the early group, 1 January 1979 for the later group of Thorotrast patients or the date the wound was inflicted for the control groups. Follow-up to 15 July 1998 or death if earlier. Follow-up was conducted via hospital records; completeness of follow-up is unclear. Causes of death identified mainly from death certificates, confirmed where possible by hospital records and postmortem examinations.	No individual estimates of exposure available. Mean amount of Thorotrast injected was 10-19 ml.	Liver Lung Leukaemia	<u>Liver</u> Overall *Years since injection* 0-9 [10]–19 20–29 30–39 40–49 50+ <u>Lung</u> Overall *Years since injection* 0-9 [10]–19 20–29 30-39 40-49 50+ <u>Leukaemia</u> Overall *Years since injection* 0-9 [10]–19 20–29 30-39 40-49 50+	143 11 10 	35.9 (24.2, 53.4) 0 6.0 (0.7, 51.8) 24.5 (9.6, 62.4) 47.9 (27.4, 83.6) 47.2 (29.9, 74.4) 25.7 (14.3, 46.1) 2.0 (1.0, 3.9) 0 0 6.0 (0.7, 49.5) 2.9 (0.7, 12.7) 2.6 (1.1, 6.2) 1.0 (0.2, 4.3) 12.5 (4.5, 34.7) 0 0 14.7 (1.4, 157.8) 0 16.2 (4.5, 58.5) 25.0 (4.9, 128.8)	Age and calendar period	In another publication from this cohort (Mori *et al.*, 1999a), among those injected with Thorotrast two cases of bone sarcoma and three cases of sarcoma and other cancers at the injection site were observed. No cases of those cancers were observed among controls. Overall mortality rate ratio (MRR) for liver cirrhosis was 6.9 (4.0, 12.0) based on 143 deaths. MRRs for different categories of years since injection were as following: 0-9: 0 [10]–19: 0 20–29: 11.4 (4.6, 28.3) 30-39: 6.7 (2.6, 17.0) 40-49: 9.2 (4.1, 20.4) 50+: 6.3 (1.3, 30.2)

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Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Liu et al. (1992) United States Thorium processing plant workers	Cohort of 3796 workers (3119 male, 677 female) employed at a thorium-processing plant between 1915 and 1973. Follow-up period: 1940-1982. Vital status ascertained primarily via the Social Security Administration, supplemented by other sources. 6.6% were lost to follow-up. Death certificates available for 93.3% of deceased cohort members	Job classification (Groups 1, 2 aqnd 3, assumed to have progressively lower thorium exposures), based on an industrial hygiene survey. Individual dose estimates were not available.			**Males**	**SMR**	Age, calendar period, gender	No association found between lung cancer mortality in male workers and job classification, duration of employment or time since first employment. Data on smoking were not available. Other than for lung cancer, no other cancer type had a significantly raised SMR.
			All cancer	Group 1 (highest)	113	1.23 (1.01-1.47)		
				Group 2	19	1.44 (0.86-2.24)		
				Group 1 (lowest)	21	1.28 (0.79-1.96)		
			Lung	Group 1 (highest)	39	1.38 (0.98-1.89)		
				Group 2	6	1.37 (0.50-2.99)		
				Group 1 (lowest)	5	1.12 (0.36-2.62)		
Chen et al. (2003) China Rare earth ore miners	Cohort of 3016 miners exposed to dusts containing thorium and of 3967 unexposed miners. Follow-up period: 1977-2001.	Measuremts of thoron-exhaled activity made for 638 exposed miners and 143 unexposed miners. The mean lung burdens were, respectively, 1.60 Bq and 0.30 Bq. Individual exposures were not available for incorporation in the epidemiological analysis.	Lung	Exposed	27	**SMR** 6.13 (4.41-8.52)	Age, calendar period (?)	Not possible to quantify the impact of smoking, nor the the effects of dust on the broncho-epithelial system.
				Unexposed	8	1.90 (0.94-3.84)		

MRR, mortality rate ratio; SMR, standardised mortality ratio