Health Effects Following Long-term Exposure to Thorium Dusts:

A Twenty-year Follow-up Study in China

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Abstract: A twenty-year follow-up study was carried out at Baiyun Obo Rare-earth Iron Mine in China. It has been operating for forty three years. It's ore contains ThO_2 at a percentage of 0.04.The purpose of this study is to investigate the possible health effects of dust-inhaled miners following long-term exposure to thorium dusts. An electrostatic collection system was used to measure the exhaled thoron activity of each examinee, through simple calculation , each examinee's thorium lung burden obtained. Health status was ascertained through questionnaire, physical examination and clinical laboratory tests. An epidemiological study on the mortality rates of lung cancers of the dust-inhaled miners and internal controls was also carried out. Results showed that the highest thorium lung burden for 1158 measurements of 638 miners was at a value of 11.11 Bq, one tenth of the maximum thorium lung burden. In a ten-year investigation on the four haematological parameters and four hepatic parameters of 638 exposed miners, no adverse effects were observed. The incidence of severe breathlessness, lung function tests, pneumoconiosis of stage O^+ and the concentration of ceruloplasmin in the serum of high thorium lung burden group are much higher than that of low thorium lung burden group. However, owing to the concentration of SiO_2(10%)are much higher than that of the ThO_2(0.04%) in the dust, the disorders of respiratory tract are mainly due to the fibrogenic effects of SiO_2. Epidemiology study showed that both the SMRs of the dust-inhaled miners and the dust-free miners are all greater than one. The SMR of the dust miners was much higher than that of the controls. The difference between these two SMRs was highly significant(x^2=9.488, P<0.005). It proved that the high SMR value of the lung cancers of dust exposed miners were due to the inhaled thorium and its short-lived thoron progeny. This was the first evidence in humans for the carcinogenicity of thorium-232 and its short-lived thoron progeny after inhalation. The total person-years of the dust-exposed miners and the controls was at a value of 62712 and 34672 respectively.

Key Words: thorium, thoron progeny, health effects, lung cancer, epidemiology, China

INTRODUCTION

A twenty-year follow-up study was carried out at Baiyun Obo Rare-earth Iron Mine in China. It has been operating for forty three years. Its ore contains not only iron, rare-earth elements and silica dioxide but also thorium .Thorium is present at 0.04%.Since 1982,we have been investigating the relationship between thorium lung burden and health effects on miners of this mine. The purpose of our investigation is to answer the following questions. How much inhaled thorium is deposited in the lungs of miners after long-term exposure? Does it exceed the maximum permissible lung burden of thorium? What are the health effects? Does it cause excess lung cancer? Does it affect lung function? Is improvement of working conditions necessary?

The total number of miners and staff members at this mine is 6983(in the year of 2001). Among them,3016 were dust-inhaled miners, 3967 were dust-free miners and staffs. In order to get more information on the carcinogenic effects of inhaled thorium and the difference between SiO_2 and ThO_2 in inducing fibrosis of lung tissue. A two-year-experiment on 680 Wister rats were carried out in parallel during the period of 1989-1991.

Therefore, in this paper two parts of information are included. One is epidemiological study and medical examinations, another one is in vivo study.

METHODS

The method used to measure exhaled thoron activity was developed in 1982 from that used at the Argonne National Laboratory in the USA (Prostendorfer and Mercer 1979; Stehney et al. 1980). It is based on electrostatic collection on to a negatively charged Mylar disc of the daughter ^{212}Pb, 85-88% of which is positively charged. The exhaled thoron activity is expressed as concentration measured at the subject's mouth. A conversion factor of 3.7 Bq emanating ^{224}Ra equivalent activity at the mouth to 37 Bq of ^{232}Th was used to estimate the thorium lung burden (Toohey et.al 1983). The true amount of thorium will tend to be higher because there may not have been time for equilibrium between thorium and ^{212}Bi to be established, because intermediate members of the decay chain, particularly ^{228}Ra and ^{224}Ra, may hare left thorium in the lungs, and because of exhalation of ^{220}Rn. In our situation, an underestimate by a factor of 2 was suggested. Due to the different conditions between Bayun Obo Mine and that of ANL, the total counting time was shortened from 30 h to 200 min, while the negative voltage on the electrode was raised from 5.8 kV to 9.0 kV. This resulted in an increase in the total efficiency from 50% to 70%. The counter background is extremely low (6 counts.d^{-1}). The overall uncertainty is strongly dependent on the value of the emanating ^{224}Ra and ranges from ±0.013 to ±0.07 Bq as the emanating ^{224}Ra and ranges from 0.037 Bq to 3.70 Bq (Table 1).

Table 1. The basic performance of the electrostatic system

Item	Value
Counter background (counts.min^{-1})	0.003
Minimum detection limit of thoron outside the body (Bq) (zero activity ±3σ)	0.007
Lower limit for the detection of thorium contamination in the miners′lungs (Bq)(^{224}Ra at the mouth)	0.068
Overall uncertainty depends on the value of the emanating ^{224}Ra at the mouth (Bq)	0.037-3.7 (±0.013-0.070)
Median variance coefficient (%)	±17

In order to evaluate the general distribution of exposure to natural thorium, a total of 130 exposed miners of the Bayun Obo mine were chosen from six dust-generating workshops by stratified random sampling. Their individual exhaled thoron activity and thorium lung burden estimate was determined using our electrostatic system in 1983.

A total of 1301 measurements of exhaled thorn activity were carried out on 781 individuals during the period 1983-1994. Of these, 1158 measurements were carried out on 638 thorium miners, 143 measurements were carried out on 143 unexposed workers(controls).

In the period 1983-1994, 1158 medical examinations were carried out on 638 dust-inhaling miners. A register of questionnaires on respiratory symptoms, a complete physical examination, ceruloplasmin tests were carried out in some of the examinees. An epidemiological study on the mortality rates of lung cancers of the dust inhaling miners and internal controls was carried out in 2001.

In vivo, cumulative dose in inducing lung cancer by thorium dioxide and the determination of concentration of ceruloplasmin in rat serum were carried out on 680 Wister male rats in a two-year-study.

RESULTS

Thorium lung burden estimates of the exposed miners and of the controls

The 130 exposed miners in 1983 were classified into eight groups according to the emanating ^{224}Ra

equivalent activity at the mouth, 122 (93.8%)of them were less than 0.11 Bq (Table 2).

Table 2. Results of measurements of exhaled thoron progeny (130 subjects) expressed as the equivalent amount of freely emanating ^{224}Ra at the mouth.

Emanating ^{224}Ra at mouth (Bq)	No of subjects
0.52~0.55	1
0.22~0.26	1
0.19~0.22	1
0.15~0.18	1
0.11~0.14	4
0.074~0.11	16
0.037~0.074	49
<0.037	57

The average value of thorium lung burden estimates for 1158 measurements of 638 exposed miners was 1.60 Bq, while the average value of thorium lung burden estimates of 143 controls was 0.30 Bq .Of the 638 exposed miners in 1983-1994,585(91.7%) of them had a thorium lung burden less than 2.22 Bq (1 investigation level, see ICRP Publication 10(ICRP 1968)). The highest value was a thorium lung burden of 11.11 Bq, which is one tenth of the permissible thorium lung recommended by ICRP Publication 10A (ICRP 1991) (Table 3).

Table 3.Summary of thorium lung burden estimates on miners (638 subjects)

Thorium lung burden estimates (Bq)	No of subjects
11.11	1
8.89~11.07	5
6.67~8.85	2
4.44~6.63	2
2.22*~4.41	43
<2.19	585

*1 investigation level=2.22Bq

Initial estimation of excess lung cancer incidence among miners exposed to thorium dusts and thoron progeny.

To simplify calculation, it was assumed that the natural thorium lung burden estimated from the exhaled thoron activity was present from the beginning of each miner's service. Thus the estimated number of excess lung cancers is probably an overestimate. As the risk of lung cancer in man due to inhalation of thorium dust and thoron progeny has not hitherto been reported, a risk range of lung cancer due to inhalation of radon and its short-lived progeny was taken from BEIR IV (U.S. NRC 1988). It is interesting to note that the excess of lung cancers due to the inhaled thoron progeny is higher than that from the inhaled thorium (Table 4). (Chen and Cheng 1998)

Table 4. Estimated excess lung cancers due to inhaled thorium dusts and thoron progeny in 2072 miners.

Period	Thorium Inhalation	Inhalation of thoron progeny*	Total increase (number of cases)

	(number of cases)	(number of cases)	
1958-9.1983	0.02-0.12	0.10-0.54	0.12-0.66
1983-9.1993	0.01-0.08	0.06-0.35	0.07-0.43
1958-9.1993	0.047-0.20	0.16-0.89	0.20-1.09
1968-1988	0.03-0.11	0.09-0.50	0.11-0.61

* The air concentrations of thoron short-lived progeny in the crushing division are in the range 4.2×10^2-6.77×10^4 MeV/L,the average is 1.08×10^4 MeV/L, higher than that of radon short lived progeny by a factor of about 10.

Estimated thorium lung burdens and relationship to radiography(Chen and Cheng 1998.)

It is interesting to note that there seems to be a probable threshold of inhaled thorium and dusts for inducing stage 0^+ pneumoconiosis (only fibrosis but no nodules apparent on the X ray film, a stage between stage 0, normal, and stage 1, pneumoconiosis).

The so-called probable threshold is the lowest value of thorium and dust lung burden of the miners suffering from pneumoconiosis stage 0^+ (table 5).

Table 5. Probable threshold of thorium-containing dusts lung burden inducing pneumoconiosis stage 0^+.

Workshop	Miners	Cases	Thorium (Bq)	Probable Dust(mg)	Threshold Year
Crushing	31	8	1.52	940*	1984
Crushing	94	26	1.30	803	1987
Mining	86	4	1.26	780	1988
Crushing	64	12	1.22	756	1994

*This number comes from: 1mg natural thorium=4.037 Bq; 1.52 Bq thorium=0.377mg. Thorium, 0.377mg×2500(the percentage of thorium in the dusts is 0.04%)=941.29 mg of dusts (~940 mg).

Comparison of lung function disorders between dust-inhaled miners and controls

Lung function tests using a Discom-21 spirometer (Chest Corporation, Japan), were carried out on 67 dust-inhaled miners and 69 controls from the same mine in 1990.The backgrounds for the two groups were comparable. A comparison of the miners with the controls was as follows: average age (47.15:47.42 years), average working history (25.34:26.01 years) , average smoking history (25.15:25.53 years), average cigarettes per day (16.80:19.07). While the differences in lung function disorders between them were very significant (Table6), it shows that lung function disorders were due to long-term inhalation of thorium-containing dusts.

Table6 Incidence of lung function disorders

Group	Number of Persons	Cases	Types		
			Obstructive	Restrictive	Mixed
Dust-inhaled Miners	67	18	8	7	3
Controls	69	0	0	0	0

Relationship between thorium lung burden and serum ceruloplasmin of mining workers

Serum ceruloplasmin is a biochemical index reflecting the fibrogenic process in human lung tissue. Our results showed that ceruloplasmin is one of the most sensitive indices for reflecting the fibrogenic process due to inhaled thorium-containing rare-earth dusts and short-lived thoron progeny(Tables 7 and 8).

Table 7 Relationship between thorium lung burden and serum ceruloplasmin.

Job	Thorium lung Burden (Bq)	Number of cases	Cerulopasmin (μ ml^{-1})(X±SE)	P*
Mining Workers	＜0.74	72	11.74±0.39	＜0.001
	0.78-1.11	11	11.44±0.74	＜0.001
	1.15-1.67	8	10.58±1.21	＜0.001
Controls	0.10-0.66	8	5.53±0.34	

*Compared with controls

Table 8 comparison of serum ceruloplasmin in mining workers and controls both having normal lung function

Job	Number of cases	Ceruloplasmin (μ ml^{-1}) (X ± SE)	P
Mining Workers	65	11.10± 0.38	＜0.01
Controls	8	5.38 ± 0.32	

Smoking habits

Information on smoking habits is essential in the analysis and interpretation of studies dealing with cancer mortality, lung function, as well as respiratory symptoms. In order to compare smoking habits,79 demolition miners and 79 dust-free miners with a similar age and working history were randomly selected .It can be seen from table 9 that the percentage of current smokers is similar between two groups, all being quite high.

Table9 Comparison of smoking habits in dust-inhaled miners and dust-free miners.

Smoking habits	Dust-inhaled group		Dust-free group	
	Cases	Percentage	Cases	Percentage
Non-smoking	16	20.25	18	22.78
Smoking				
Slight[a]	12	15.19	9	11.39
Medium[b]	24	30.38	6	7.60
Serious[c]	27	34.18	46	58.23
Total	79	100.00	79	100.00

[a]≤10 cigarettes/day. [b]10-20 cigarettes/day.[c]≥20 cigarettes/day.

Lung cancer mortality among dust-inhaled miners and dust-free miners

An epidemiology study on lung cancer mortality of both the dust-inhaled miners and dust-free miners and staffs was carried out in 2001. The main results were listed in Table 10.

Table 10 Standard mortality ratios(SMR)of lung cancers (1977-2001.3)

Group	Expected	Observed	SMR	95%Limits
Dust exposed Miners	4.406	27	6.13	4.41-8.52
Controls	4.201	8	1.90	0.94-3.84

Table 10 showed that both the SMRs of the dust-inhaled miners and the dust-free miners were all greater than 1.The SMR of the miners was much higher than that of the controls. The difference between these two SMRs was highly significant(X^2=9.488,P<0.005).It proved that the high SMR value of the lung cancers of dust exposed miners were due to the inhaled thorium and its short-lived thoron progeny.

The total person-years of the dust exposed miners and the controls was at a value of 62712 and 34672 respectively.

Health protection measures and results

The authors advised this mine to apply the following protection measures.(1)Devices for ventilation and prevention of dust should be improved.(2)Instructions for use of individual protection appliances should be promoted.(3)Participation in popular sports should be encouraged. It was observed that in this mine the amount of thorium deposited in the lungs of workers who habitually run was generally low .(4)Job rotation is suggested for those having an estimated thorium lung burden higher than 4.44Bq.

These measures achieved positive results. The average air concentrations of thorium dust in the main workshops and the average thorium lung burden estimates of the thorium dust –inhaling miners decreased by a factor of 20 and 3 respectively between 1983 and 1991.

Owing to the probable underestimation of thorium lung burden, all the values of thorium lung burden estimates in this paper could be doubled.

Cumulative radiation dose in inducing lung cancer by intratracheally administration thorium dioxide and its histopathological characteristics(Chen X.A. et.al 1995).

680 Wister male rats (weight 200-250 grams)were involved in this two-year-study .Th-dusts of different specific radioactivity (different amounts of thorium dioxide were added to the dust)were administered into 480 rats intratracheally. The amount of Th-dust once administered was 50mg in 1ml saline (table 11).

Table 11 Cumulative absorbed dose (in 24 months) to the rat lung of different groups

Group	Type of Contaminant	Cumulative dose (Gy)	Number of Rats
0	Controls (blank)	—	200
1	Saline	—	80
2	Th-dust	3.74×10^{-4}	80
3	Th-dust+1%ThO_2	1.01×10^{-2}	80
4	Th-dust+6%ThO_2	8.05×10^{-2}	80
5	Th-dust+18%ThO_2	1.49×10^{-1}	80
6	18 mg ThO_2	3.50×10^{-1}	80

20% of the rats of each of the seven groups were killed at of 6 months ,12 months ,18months and 24 months after administration .All the lungs and pulmonary lymph nodes were weighted and observed macroscopically and microscopically (using binocular microscope and electron microscope).The results are shown are shown in Table 12.

Table 12 .Lung tumor prevalence% at different durations after administration

Group	12months			18months			24months		
	Rats	Cases	%	rats	cases	%	rats	cases	%
0(blank)	9	1	11.1	9	1	11.1	12	2	16.7
1(saline)	10	1	10.0	9	3	33.3	13	2	15.4
2(Th-dust)	11	0.0	0	9	1	11.1	12	3	25.0
3(..-1%ThO_2)	9	0	0.0	8	1	12.5	6	0	0
4(..-6%ThO_2)	9	0	0.0	10	2	20.0	18	4	22.2
5(..-18%ThO_2	10	1	10.0	11	1	9.1	9	5	55.6
6(18mgThO_2)	10	3	30.0	10	2	20.0	14	9	64.4**
Total	88	6	8.8	66	11	16.8	84	25	29.8

**Compared with group 0,P<0.05;Compared with group 1.P<0.01.

Table 12 shows that the lung cancer prevalence increased with the duration of experiment. The highest rat lung tumor prevalence appeared in group 6 at the duration of 24 months and only this lung tumor prevalence(64.4%)was significantly different from the one of group 0(16.7%),and group 1(15.4%)at the same duration .The total number of lung tumors was 42,among them 39 were cancers.7 types of rat lung tumors were observed in this study .They were adenocarcinoma (9).squamous cell carcinoma (2), lymphoma (22),squamous adenocarcinoma (2), undifferential lung cancer (4), fibroma(2) and adenoma(1).

Effects of thorium dioxide and thorium containing rare-earth iron dusts on ceruloplasmin concentration in rat serum .

Ceruloplasmin is a sensitive biochemical index that reflects the fibrogenic process of lung tissue .At 6 months ,12 months,18 months and 24 months after intratracheal administration with Th-dusts of different specific activity.10 rats from each group were randomly selected and killed. Venous blood of each rat was collected and serum ceruloplasmin concentration was measured. Results are shown in Table 14.

Table 13 indicates the interesting fact, that the fibrogenic ability of 18mg ThO_2(group 6)is almost equivalent to that of 50mg thorium containing rare-earth iron dusts (group2).

Table 13.Ceruloplasmin concentration in rat serum of different group with different durations after administration(μg/ml)

Group	6months		12months		18months		24months	
	n	mean±SD	n	mean±SD	n	mean±SD	n	mean±SD
0(blank)	10	7.1±0.9	10	13.9±3.6	10	17.0±4.9	17	19.3±5.4
1(saline)	10	7.0±1.5	10	14.4±2.3	11	19.7±5.6	18	18.5±3.5
2(Th-dust)	10	10.2±1.5*	10	20.8±7.9*	9	18.1±5.1	13	19.1±3.6
3(..+1%ThO_2)	10	10.8±3.2**	10	19.0±5.0*	8	17.0±2.9	6	18.3±4.5
4(..+6%ThO_2)	10	10.6±1.8**	10	15.8±2.3	10	16.1±3.6	17	22.0±2.0
5(..+18%ThO_2)	10	9.7±3.6*	10	16.3±2.6	10	15.8±4.1	9	18.1±4.7
6(18mgThO_2)	10	10.6±2.8**	10	18.2±3.6*	10	22.4±7.9	14	18.8±3.8

*P<0.05**P<0.01 (compared with group 0)

CONCLUSION

The Results of twenty-year Follow-study in Baiyun Obo Rare-earth Iron Mine showed that the highest thorium lung burden for 1158 measurements of 638 miners was at a value of 11.11Bq , one tenth of the maximum thorium lung burden .In a ten-year investigation on the four haematological parameters and four hepatic parameters of 638 exposed miners, no adverse effects were observed. The incidence of severe breathlessness, lung function tests, pneumoconiosis of stage O^+ and the concentration of ceruloplasmin in the serum of high thorium lung burden group are much higher than that of low thorium lung burden group. However, owing to the concentration of SiO_2(10%)are much higher than that of the ThO_2(0.04%)in the dust, the disorders of respiratory tract are mainly due to the fibrogenic effects of SiO_2.

An epidemiological study on lung cancer mortality showed that the SMR of the dust exposed miners was much higher than that SMR of the controls (6.13 vs 1.90).The difference between these two SMRs was highly significant (X^2=9.488,P<0.005) **This was the first evidence in humans for the carcinogenicity of thorium-232 and its short-lived thoron progeny after inhalation (Chen X.A. 2001).**

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