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UR-590

THE INHALATION TOXICITY OF INDIUM SESQUIOXIDE IN THE RAT

by

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THE UNIVERSITY OF ROCHESTER
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ROCHESTER, NEW YORK

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U N C L A S S I F I E D

UR-590

Biology and Medicine
TID-4500, (15th Ed.)

THE UNIVERSITY OF ROCHESTER
Atomic Energy Project
P. O. Box 287, Station 3
Rochester 20, New York

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Contract W-7401-eng-49 between the U. S. Atomic
Energy Commission and the University of Rochester,
administered by the Department of Radiation Biology
of the School of Medicine and Dentistry.

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Date Completed: 2/10/61

Date of Issue: 5/10/61

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THE INHALATION TOXICITY OF INDIUM SESQUIOXIDE IN THE RAT

ABSTRACT

Fifty-four albino rats were exposed to a submicronic aerosol of indium sesquioxide dust for three months. This material (In_2O_3) is moderately toxic when inhaled at relatively high concentrations (64 mg/m^3). Evidence of chemical toxicity was found in body weight changes, in the hematological picture and in the gross and histological condition of the lungs and tracheobronchial lymph nodes.

The retention of indium in the tissues was followed in serially sacrificed animals. An appreciable accumulation occurred in the lungs and tracheobronchial lymph nodes. Average values for these tissues increased from 490 and 250 $\mu\text{g In/g}$ fresh tissue, respectively, after two weeks of exposure, to 1000 and 1300 $\mu\text{g/g}$ after 12 weeks. Post-exposure data indicate that approximately 58 per cent of the indium had been mobilized from the lungs and 69 per cent from the tracheobronchial lymph nodes, 12 weeks after termination of exposure.

For other tissues, i.e., liver, kidney and spleen, the indium content was low. After two weeks of exposure, average values were as follows: liver, 0.33 $\mu\text{g/g}$; kidney, 1.8 $\mu\text{g/g}$; and spleen, 0.25 $\mu\text{g/g}$. Later in the experiment, viz., 12 weeks post-exposure, the content increased 40-fold in the liver, 6-fold in the kidney, and 80-fold in the spleen. In the interval from the fourth week of exposure to the end of the post-exposure period, there was a 20-fold increase in the indium content of bone.

THE INHALATION TOXICITY OF INDIUM SESQUIOXIDE IN THE RAT

INTRODUCTION

The increased use of indium has necessitated further investigation of the toxicity and of the biological fate of this element and some of its compounds. To supplement information already obtained at this laboratory (1, 2, 3, 4), an experiment was conducted to determine the toxicity of indium sesquioxide (In_2O_3) when inhaled by the rat.

MATERIALS AND METHODS

Indium sesquioxide (In_2O_3) in the form of a finely divided yellow dust was obtained from a commercial source*. The test material was used as it was received; no attempt was made to alter particle size.

The In_2O_3 dust was dispersed from a Wright Dust Feed Mechanism (5) into the inlet air system of an exposure chamber having an internal capacity of approximately one cubic meter. The exposure apparatus will be described in detail elsewhere.

Animal exposure conditions are summarized in Table I. The atmospheric concentration of In_2O_3 dust averaged 64 mg/m^3 as determined by gravimetric analysis of filter paper** dust samples taken each hour during exposure. Individual hourly dust concentrations are plotted graphically in Figure 1. During the 224 hours of exposure the concentration ranged from 24 to 97 $\text{mg In}_2\text{O}_3/\text{m}^3$.

* The Indium Corporation of America, Utica, New York.

** Millipore filter paper obtained from Millipore Filter Corporation, Watertown 72, Massachusetts was used.

TABLE I

SUMMARY OF CONDITIONS OF EXPOSURE OF RATS TO In_2O_3 DUST

Duration, Calendar Months-	3
Exposure Schedule	
Hours/Day-	4
Days/Week-	5
Dust Concentration, mg $\text{In}_2\text{O}_3/\text{m}^3$	
Average-	64
Range-	24-97
Particle Size	
Average CMD, Microns-	0.182
Average σ_g -	2.06
Average Calculated MMD -	0.63
Average σ_g -	1.81
Temperature, Degrees Fahrenheit	
Daily Average-	74
Range-	65-80
Relative Humidity, Per Cent	
Daily Average-	60
Range-	40-84

FIGURE 1. Chamber Dust Concentration vs. Exposure Time.

The relation between the dust load on the filter papers and the quantity of In_2O_3 present was checked by analyzing spectrographically one sample daily for indium. The average recovery of indium calculated as In_2O_3 , corresponded to 96 per cent of the dust load determined gravimetrically.

The particle size distribution of the dust in the test chamber was determined in samples taken with a thermal precipitator, shadowed with chromium at 45° and photographed in an electron microscope. Characteristics of the aerosol are shown in Table I.

During the course of the experiment the temperature of the air within the chamber varied between 65 and 80°F. , the relative humidity between 40 and 84 per cent. As shown in Table I, the average temperature was 74°F. and the average relative humidity, 60 per cent.

A total of 54 albino rats (27 males and 27 females) was exposed to the In_2O_3 dust. All were young adults from the Wistar-derived (1923) Project Colony. Twenty rats of each sex and of the same age were maintained as controls. Preceding the exposure, the animals were conditioned in the chamber for approximately one month. During this time they were subjected to conditions similar to those during exposure, except that In_2O_3 dust was not present, and data were obtained that provided control values for hematology. During the dust exposure, body weight, mortality, and clinical appearance of the animals were recorded.

Pairs of rats of each sex were sacrificed by ether inhalation at exposure weeks 2 , 4 , 7 , and 12 (termination of exposure). Similar groups of control rats were handled in the same manner. Prior to sacrifice,

blood samples were taken from each experimental animal for hematological study. At 12 weeks post-exposure the remaining animals comprising six exposed rats and four control animals were sacrificed.

At sacrifice, the rats were examined grossly and the lungs were weighed. Sections of the lungs, tracheobronchial lymph nodes (PLN), liver, kidney, spleen, and femur were fixed in Bouin's solution for histopathological study. Portions of these tissues were reserved for spectrographic determination of the indium content.

RESULTS

Mortality.

A total of 13 experimental rats comprising seven males and six females died during the 3-month exposure to In_2O_3 . One rat of each sex died in the control group. The significance of the higher mortality in the indium-exposed animals is difficult to assess because various inter-current infections, principally acute purulent pleurisy and pericarditis, were the usual causes of death.

Body Weights.

The body weight data for males and females are tabulated in Tables II and III, respectively. Average body weights are plotted graphically in Figures 2 and 3. A marked growth depression observed in the experimental male rats is evident, Figure 2. This depression became evident between the first and second months of exposure and persisted throughout the post-exposure period. It reached a maximum during the

TABLE II

BODY WEIGHT RECORD - MALE RATS

Calendar Time	No. Rats	EXPERIMENTALS		No. Rats	CONTROLS	
		Body Wt., gms.			Body Wt., gms.	
		Average	Range		Average	Range
3 wks. pre-exp.	26	190	158-248	--	-	-
12 days pre-exp.	26	175	133-231	20	230	178-280
1 wk. pre-exp.	26	200	134-265	19	235	183-280
1 exp. day	26	230	191-293	19	245	194-285
1 exp. wk.	26	250	207-328	19	265	214-303
3 exp. wks.	22	265	213-337	16	275	219-321
5 exp. wks.	16	270	216-360	14	285	232-339
7 exp. wks.	14	280	232-350	14	295	251-359
9 exp. wks.	8	265	242-326	12	305	268-360
11 exp. wks.	7	265	240-334	12	320	283-380
1 wk. post-exp.	3	250	237-261	10	340	292-403
4 wks. post-exp.	3	254	231-268	10	345	294-415
7 wks. post-exp.	2	272	264-279	10	355	301-427
12 wks. post-exp.	2	284	284-284	2	362	316-408

TABLE III
BODY WEIGHT RECORD - FEMALE RATS

Calendar Time	No. Rats	EXPERIMENTALS		No. Rats	CONTROLS	
		Body Wt., gms.			Body Wt., gms.	
		Average	Range		Average	Range
3 wks. pre-exp.	28	145	110-175	-	-	-
12 days pre-exp.	28	130	102-180	20	160	140-200
1 wk. pre-exp.	28	155	119-186	20	162	139-202
1 exp. day	28	170	138-203	20	170	138-211
1 exp. wk.	28	180	144-214	20	180	147-208
3 exp. wks.	19	188	141-214	18	190	157-234
5 exp. wks.	13	193	161-224	16	195	160-242
7 exp. wks.	11	197	153-227	15	200	167-244
9 exp. wks.	8	210	179-230	13	202	172-250
11 exp. wks.	6	215	175-233	13	209	176-259
1 wk. post-exp.	4	208	174-239	11	223	204-272
4 wks. post-exp.	4	206	176-239	11	225	201-272
7 wks. post-exp.	4	212	181-249	10	226	202-247
12 wks. post-exp.	4	209	184-244	2	226	224-228

FIGURE 3. Body Weight Curves - Female Rats.

first post-exposure month when the body weights of the experimental males averaged 90 grams less than those of the controls. The slight recovery in growth during the latter part of the post-exposure period is of questionable significance because of the few (two) surviving animals.

No adverse effects on the growth of the experimental female rats were observed.

Hematology.

Blood samples were taken from the rats pre-experimentally and at time of sacrifice. The average hematological values are presented in Table IV. The only evidence in these data of any effect on the blood picture from the inhalation of In_2O_3 was a 2- to 3-fold increase in the absolute neutrophil count. The average absolute neutrophil count for the experimental males and females was 4,592 and 6,483, respectively, during the pre-exposure period. After two weeks of exposure to In_2O_3 these values increased to 11,741 and 13,048, respectively. This alteration in the differential white cell count continued throughout the post-exposure period; at 12 weeks post-exposure the average values were as follows: 13,414 for male rats, 13,308 for female rats.

Lung Weights and Lung Weight-Body Weight Ratios.

At sacrifice the weights of the lungs of the experimental and control rats were recorded and the organ weight-body weight ratios calculated. This information is tabulated in Tables V and VI. The lungs of the experimental males (Table V) and females (Table VI) were from three to five times heavier than those of the controls. These findings were reflected in the lung-weight-body weight ratios which for the experimental animals were approximately five times greater than the controls.

TABLE IV
AVERAGE HEMATOLOGICAL VALUES

Time	No. Rats	Body Weight (gms)	Hgb. gm/100cc.	Hemato- crit %	Retic. %	Platelets x 100,000	WBC	Absolute Neutrophil Count	Absolute Lymphocyte Count
MALE RATS									
3 wks. pre-exp.	10	178	15.9	55.8	3.4	6.7	20,375	4,592	14,759
2 wks. exp.	2	262	15.8	55.3	4.5	8.9	30,650	11,741	17,573
4 wks. exp.	2	273	17.8	64.5	2.6	10.5	27,150	8,990	17,404
7 wks. exp.	2	335	16.3	56.5	4.9	10.1	30,435	14,392	15,211
12 wks. exp.	2	311	16.3	58.8	3.3	8.4	36,400	15,653	15,649
12 wks. post-exp.	2	284	15.5	54.3	4.0	8.1	27,825	13,414	13,299
FEMALE RATS									
3 wks. pre-exp.	12	140	15.8	55.4	3.3	6.2	25,013	6,483	17,635
2 wks. exp.	2	197	12.8	46.0	9.6	8.3	24,725	13,048	10,853
4 wks. exp.	2	199	14.6	51.0	6.3	12.8	40,125	15,649	23,051
7 wks. exp.	2	186	14.0	49.5	6.6	9.8	30,300	14,676	14,392
12 wks. exp.	2	218	15.0	51.3	5.5	8.2	32,575	12,724	16,064
12 wks. post-exp.	4	209	15.4	52.8	4.5	7.8	30,625	13,308	12,783

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TABLE V
LUNG WEIGHTS AND LUNG WEIGHT-BODY WEIGHT RATIOS

Male Rats

Time	No. Rats	Body Wt., gms.		Lung Wt., gms.		Lung Wt.-Body Wt. Ratio*	
		Average	Range	Average	Range	Average	Range
CONTROLS							
7 wks. exp.	2	320	280-359	1.39	0.96-1.81	4.24	3.43-5.04
12 wks. exp.	2	322	300-344	1.26	1.19-1.33	3.71	3.44-3.97
12 wks. post-exp.	2	362	316-408	1.65	1.52-1.78	4.59	4.36-4.81
EXPERIMENTALS							
7 wks. exp.	2	335	320-345	5.99	5.17-6.80	17.8	16.1-19.4
12 wks. exp.	2	311	274-347	5.92	5.47-6.36	19.5	15.8-23.2
12 wks. post-exp.	2	284	284-284	6.41	6.28-6.54	22.6	22.1-23.0

* mg lung/gm body weight.

TABLE VI
LUNG WEIGHTS AND LUNG WEIGHT-BODY WEIGHT RATIOS

Female Rats

Time	No. Rats	Body Wt., gms.		Lung Wt., gms.		Lung Wt.-Body Wt. Ratio*	
		Average	Range	Average	Range	Average	Range
CONTROLS							
7 wks. exp.	2	218	217-218	1.13	1.05-1.20	5.16	4.79-5.53
12 wks. exp.	2	191	176-205	1.11	0.91-1.31	5.78	5.17-6.39
12 wks. post-exp.	2	226	224-228	1.06	1.02-1.10	4.69	4.47-4.91
EXPERIMENTALS							
7 wks. exp.	2	186	178-194	3.44	3.15-3.72	18.4	17.7-19.1
12 wks. exp.	2	218	208-228	5.53	5.31-5.75	25.5	23.3-27.6
12 wks. post-exp.	4	209	184-284	4.43	3.76-4.98	21.3	19.2-23.4

* mg lung/gm body weight.

Indium Content of Tissues.

Portions of selected tissues from rats sacrificed at various intervals during the experiment were analyzed spectrographically for indium. Average indium concentrations and ranges, expressed in micrograms of indium per gram of fresh tissue ($\mu\text{g/g}$) are given in Table VII. As seen in this table, the lungs and PLN contained by far the most indium. Average values for these tissues (lung and PLN) increased from 490 and 250 $\mu\text{g/g}$, respectively, after two weeks of exposure to 1000 and 1300 $\mu\text{g/g}$ after 12 weeks. Post-exposure data (lung: 420 $\mu\text{g/g}$, PLN: 410 $\mu\text{g/g}$) indicate that approximately 58 per cent of the indium had been mobilized from the lung and 69 per cent from the PLN, 12 weeks after termination of exposure.

For other tissues, i.e., liver, kidney, and spleen the indium content was low. After two weeks of exposure average values were as follows: liver, 0.33 $\mu\text{g/g}$; kidney, 1.8 $\mu\text{g/g}$; and spleen, 0.25 $\mu\text{g/g}$. Later in the experiment, viz., 12 weeks post-exposure, the indium content increased 40-fold in the liver, 6-fold in the kidney and 80-fold in the spleen.

In the bone, deposition occurring between four weeks and the end of the post-exposure period represented a 20-fold increase in the indium content.

In Figure 4 indium concentrations in the tissues are plotted on a log scale against time on a linear abscissa. From the lung and PLN curves (Figure 4) one can estimate the biological half-time for indium to be 2 1/2 months in the lung and 1 3/4 months in the PLN. These estimations

TABLE VII

INDIUM CONTENT OF TISSUES OF RATS EXPOSED TO In_2O_3 DUST

Values in Micrograms of In per Gram Fresh Tissue

Organ		No. Rats	4	4	4	4	6
		Time Cal. Wks.	2	4	7	12*	24**
Lung	Mean		490	650	360	1000	420
	Range		390-600	600-750	210-460	610-1500	260-580
PLN***	Mean		250	850	1100	1300	410
	Range		110-450	470-1200	760-1200	260-2600	140-800
Kidney	Mean		1.8	3.3	6.3	9.2	12.0
	Range		0.77-2.8	1.6-4.9	4.3-7.7	7.5-11	7.3-14
Liver	Mean		0.33	1.3	3.5	3.1	11
	Range		0.24-0.41	0.46-1.8	1.5-6.6	2.2-4.2	8.1-15
Spleen	Mean		0.25	2.5	4.3	16	21
	Range		0.08-0.49	0.43-6.3	1.3-8.0	10-23	12-37
Femur	Mean		--	0.20	0.75	3.4	4.0
	Range		--	0.00-0.40	0.00-1.2	1.7-4.5	1.4-6.0

* Termination of exposure

** 12 weeks post-exposure

*** tracheobronchial lymph nodes

FIGURE 4. Indium Content of Rat Tissues vs. Time.

indicate that In_2O_3 is mobilized from the lung and PLN at a much faster rate than are the "insoluble" oxides of beryllium, thorium, or uranium. It is interesting to note that mobilization of indium from the lungs and PLN during the post-exposure period is reflected, at least in part, by the increased indium content of the kidney, liver, bone and spleen. The tissues of control rats were essentially free of indium.

Pathology.

The only gross findings seeming to result from inhaling In_2O_3 dust were increase in lung weight, increase in consistency of the lungs and enlargement of the tracheobronchial lymph nodes.

Microscopic Findings: Lesions observed that could be attributed to the inhalation of In_2O_3 were limited to the lungs and tracheobronchial lymph nodes. In all of the lungs examined at the various time periods there was present in the alveoli a peculiar eosinophilic, granular, probably protein-containing, fluid (Figures 5, 6 and 7). There was wide distribution of the fluid throughout the lung; however, areas of air-containing alveoli, sometimes emphysematous, were present. The fluid was also seen in some of the terminal bronchi. A few cells, viz., alveolar phagocytes and polymorphonuclears, were always present in the fluid in addition to some nuclear debris. In some lungs small foci of consolidation, made up mostly of polymorphonuclears, were observed (Figure 8). The alveolar phagocytes, with both vacuolated and non-vacuolated cytoplasm, were present either resting on the alveolar wall or free in the fluid (Figures 6 and 7). Frequently edema about the large vessels was seen.

The alveolar walls were rather markedly altered. Many foci were observed in which the alveolar wall appeared to consist of an avascular

FIGURE 5. Lung (H and E Mag. x150) 12 weeks post-exposure.

FIGURE 6. Lung (H and E Mag. x300) 2 weeks exposure.

FIGURE 7. Lung (H and E Mag. x 300) 7 weeks exposure.

FIGURE 8. Lung (H and E Mag. x150) 7 weeks exposure.

strand of spindle-shaped elongated cells made up mostly of cytoplasm and a few nuclei (Figures 5 and 6). Large round cells, probably either alveolar phagocytes or alveolar epithelial cells, were seen resting on this membrane. In other areas the alveolar walls were lined by large, ovoid or cuboidal cells presumably alveolar epithelium (Figure 7). The character of the lesions remained, in general, much the same regardless of the period of exposure. In the lungs of the animals sacrificed 12 weeks after cessation of exposure the extent of edema and exudation was somewhat less than that seen previously (Figure 5).

A yellowish staining particulate material could be seen in the lungs and tracheobronchial lymph nodes after seven weeks exposure; this became more prominent in the nodes as time went on and was greatest in animals sacrificed 12 weeks post-exposure (Figure 9). The lymph nodes from all exposed animals were enlarged, and this enlargement seemed to be a result of hyperplasia of the lymphoid elements; however, the germinal centers were about normal in size.

Fourteen of the experimental animals exhibited acute purulent pleurisy and pericarditis. The kidneys of two animals showed mild interstitial nephritis. Focal necrosis of the liver was observed in two animals.

DISCUSSION

The results of this study clearly indicate that In_2O_3 , when inhaled at relatively high concentrations (64 mg/m^3) can produce toxic manifestations in rats. Evidence of chemical toxicity was found in body weight

FIGURE 9. Tracheobronchial Lymph Node (H and E Mag. x300)
12 weeks post-exposure.

changes in male rats, in the hematological picture, and in the gross and histological condition of the lungs and tracheobronchial lymph nodes.

Mortality during the 3-month exposure period, was approximately six times greater in the indium-exposed animals than in the control group. It is difficult to say with any degree of certainty that the mortality figures directly reflect the toxicity of indium because various intercurrent infections were the usual causes of death in the experimental group. Whether the exposure to indium increased the incidence or severity of these diseases is an unanswered question. Further work should be done to resolve this important point.

Another important physiological property of indium is its mobility. In this experiment, inhaled In_2O_3 was mobilized from the primary site of deposition, the lung at a faster rate and possibly in a different manner, than are the "insoluble" oxides of beryllium, thorium, or uranium. This is borne out by the relatively short biological half-time of 2 1/2 months for In_2O_3 in the lungs of rats, as compared to estimations of 6 to 8 months for BeO , ThO_2 , and UO_2 . This difference might be related to the increased solubility of In_2O_3 in body fluids, and/or the smaller particle size of the airborne indium trioxide dust.

The most striking evidence of the physiological activity of In_2O_3 was the changes observed in the lungs of the indium-exposed animals. These lungs were three to five times heavier than those of the controls. Upon microscopic examination, lesions were observed that were probably inflammatory in character. However, they differed from the usual inflammatory reaction in the relative paucity of inflammatory cellular exudate. It is somewhat odd (1) that the lesions changed little over

the periods of exposure and post-exposure and (2) that there was no fibrosis resulting from the healing process. In a few of the lungs from the 3-month post-exposure group a few small foci of early fibrosis were seen; however, it is difficult to attribute this with certainty to the treatment received.

SUMMARY

1. Indium sesquioxide (In_2O_3) is moderately toxic when inhaled by rats.
2. In a 3-month dust exposure, at a level of $64 \text{ mg } \text{In}_2\text{O}_3/\text{m}^3$, signs of chemical toxicity included growth depression in male rats, abnormalities in hematological values, and changes in the gross and histological condition of the lungs and tracheobronchial lymph nodes.
3. Retention of indium following inhalation of In_2O_3 dust was primarily in the lungs and tracheobronchial lymph nodes. These tissues averaged 1000 and 1300 $\mu\text{g In/g}$ fresh tissue, respectively, after three months of exposure. Only a small fraction of the inhaled indium appeared in the other tissues examined; the spleen was highest with an average value of 16 $\mu\text{g/g}$, followed, in order, by the kidney (9 $\mu\text{g/g}$), the bone (3 $\mu\text{g/g}$) and the liver (3 $\mu\text{g/g}$).
4. Indium is mobilized from the site of entry into the body, and distributed to other tissues and probably excreted in urine and feces. For example, three months following exposure the distribution of indium in the body was as follows: lungs, 420; tracheobronchial lymph nodes, 410; spleen, 21; kidney, 12; liver, 11 and bone, 4 $\mu\text{g In/g}$, respectively.
5. Under the conditions of this experiment the biological half-time for In_2O_3 in the lungs of rats was estimated to be about 2 1/2 months.

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