P-62-332

TITANIUM DIOXIDE YRC
(Contaminated With ca 1% Sb_2O_3 + 1% Al_2O_3)

Reaction 14 Days After Intratracheal Introduction

Male CRCD Rats

MR-583 - H-3106

Data garnered at necropsy and through histologic examination are assembled in Tables 1 to 6 and permit the following inferences:

(a) An appreciable amount of the test substance has been retained in the lung and is being sealed off in such a manner that prolonged interaction with the respiratory surfaces seems likely.

(b) The epithelization of the alveolar septa and the focal deposition of collagen may be viewed with suspicion. Such changes so soon after the introduction of the metal oxides are likely to result in persistent and progressive pulmonary reactions.

(c) The response is more severe than that caused by TiO_2 which does not contain the antimony contaminant. It would seem, therefore, that the latter may be pathogenic.

(d) More pigment has been retained in the lymphoid tissue and the latter has undegone hyperplasia. The Sb_2O_3 is, therefore, likely also to affect this system.

CONCLUSION

This is not an inert material, and the Sb_2O_3 contaminant probably is the pathogenic agent.

G. W. H. Schepers, M.D.

GWHS/ah
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TABLE 1

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TITANIUM DIOXIDE (IMPURE)

YRC

BIOLOGICAL ACTION 14 DAYS AFTER INTRATRACHEAL INJECTION

MALE CRCD RATS

NECROPSY FINDING

Group	Rat No.	1	2	3	4	5	6	7	8
TiO_2	50254	+	-	+	-	-	-	-	-
1 ml of 5% suspension	57	-	++	-	-	+	-	-	-
In Normal Saline	65	-	++	-	-	+	-	-	-
	66	-	-	+	++	++	++	++	-
Control	50291	+++	-	-	-	-	-	-	a
1 ml Normal	300	++	-	-	-	-	-	-	b
Saline Only	316	++	-	-	-	-	-	-	c
	317	++	-	-	-	-	-	-	-

1. Lungs: Irregular congestion and sub-pleural plaques
2. Lungs: White material predominantly in right lower lobe
3. Lungs: White material throughout lungs
4. Lungs: Hyperinflated
5. Lymph Nodes: Enlarged and impregnated with white material
6. Liver: Edematous
7. Thymus: Hypothophy
8. Coincidental Lesions: (a) Hydronephrosis right kidney (b) Kidney surface speckled (c) Testes congested

\+ Slight
++ Moderate
+++ Marked

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TABLE 2

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TITANIUM DIOXIDE (IMPURE)
YRC

METRICAL DATA - AVERAGES

Group	Body Weight Init.	Body Weight Final	Brain	Heart	Lungs	Liver	Pancreas	Stomach	Spleen	Kidneys	Testes	Thymus
ORGAN WEIGHTS												
Test	366	410	2.01	1.27	2.58	15.7	.68	1.67	.70	3.12	3.33	.56
Control	360	408	2.08	1.28	1.49	16.3	.86	1.78	.72	3.22	3.18	.57
RATIOS*												
Test		410	.49	.31	.64	3.8	.16	.40	.17	.76	.81	.13
Control		408	.51	.31	.36	4.0	.21	.44	.18	.79	.78	.14
DEVIATION OF RATIOS FROM CONTROL VALUES												
Deviation %			- 4	0	+ 78	- 5	- 24	- 9	- 6	- 4	+ 4	+ 7

* $\frac{\text{Organ Weight}}{\text{Body Weight}}$ x 100

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TABLE 3

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TITANIUM DIOXIDE (IMPURE) YRC

BIOLOGICAL ACTION AFTER INTRATRACHEAL INJECTION

MALE CRCD RATS

HISTOLOGY OF LUNG

Group	Rat No.	Focal Detelectasia	Pigment Alevolar	Phagocytosed & Transported	Alveolar Catarrh	Septal epithelization	Collagen Deposits	Lymphoid Hyperplasia RES	Bronchiolitis & Bronchitis	Vascularity Increased	Perivascular infiltration	Hypertrophy Pulmonary Blood vessels	Tracheitis
Ti O_2 1 ml of 5% suspension in Normal Saline	50254	++	+++	(+)	++	++	+	+++	++	++	+++	+	+
	57	-	-	-	-	-	+	-	(+++)	+	+	-	++
	65	+	++	+	+	+	-	++	+	+	+	++	+
	66	++	+++	++	++	++	++	++	-	++	++	+	+
Control 1 ml Normal Saline	50291	-	-	-	-	-	-	+	+	-	+	-	+
	300	-	-	-	-	-	-	+	+	-	+	-	-
	316	-	-	-	-	-	-	+	+	-	++	-	++
	317	-	-	-	-	-	-	+	-	-	++	-	+

RES - (Predominantly of the reticuloendothelial component)

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TABLE 4
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TITANIUM DIOXIDE (IMPURE)
YRC

HISTOLOGY: OTHER ORGANS

Rat No.	Brain 1	Liver 2	Kidney 3	Testes 4	Thymus 5	Spleen 6	Lymph Nodes 7	Bone Marrow Pancreas Alimentary Tract
50254	-	+	-	++	+	+	++	NAD
50257	+	-	-	+	++	-	+	"
50265	+	+	-	+	+	+	++	"
50266	-	-	-	+	-	-	++	"
50291	+	-	-	+	-	-	-	"
50300	-	-	+	+	-	-	-	"
50316	+	-	-	++	-	-	-	"
50317	+	-	-	+	+	-	-	"

+ = Slight ++ = Moderate reactions. NAD = No abnormality detected.

1 = Oligodendroglial vacuolation.
2 = Centrilobular congestion.
3 = Focal nephron degeneration.
4 = Hypospermia.
5 = Congestion of medulla.
6 = Extraneous pigment without any surrounding tissue reaction.
7 = Extraneous pigment with associated hyperplasia of reticuloendothelial component.

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TABLE 5
H-3106 - MR-583

TITANIUM DIOXIDE (IMPURE)
YRC

Biological Action 14 Days After Intratracheal Injection

ORGAN WEIGHTS

Group	Rat No.	Body Weight Init.	Body Weight Final	Brain	Heart	Lungs	Liver	Pancreas	Stomach	Spleen	Kidneys	Testes	Thymus
TiO_2 1 ml 5% Suspension in Normal Saline	50254	365	412	2.01	1.29	2.54	15.79	.55	1.69	.62	2.92	3.22	-
	50257	375	434	1.92	1.20	1.61	16.41	.85	1.79	.87	2.91	3.25	.83
	50265	378	413	2.10	1.38	3.19	16.43	.62	1.63	.74	3.29	3.47	.43
	50266	348	383	2.00	1.21	2.98*	14.33	.71	1.58	.57	3.35	3.39	.41
Control 1 ml of Normal Saline	50291	360	413	2.10	1.45	1.61	16.87	.64	-	.81	3.21	3.42	.48
	50300	380	430	2.11	1.30	1.51	15.40	1.22	1.69	.63	3.40	3.51	.68
	50316	348	389	2.11	1.25	1.22	15.73	1.10	1.75	.69	2.95	1.95	.64
	50317	350	402	1.99	1.11	1.63	17.21	.48	1.89	.73	3.31	3.85	.48

* Enlarged and filled (photographed)

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TABLE 6

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TITANIUM DIOXIDE (IMPURE) YRC

BIOLOGICAL ACTION AFTER INTRATRACHEAL INJECTION

MALE CRCD RATS

ORGAN WEIGHT RATIOS

Group	Animal No.	Body Weight Final	Brain	Heart	Lungs	Liver	Pancreas	Stomach	Spleen	Kidneys	Testes	Thymus
Ti O_2 1 ml of 5% suspension in Normal Saline	50257	434	.44	.28	.37	3.8	.20	.41	.2	.67	.75	.19
	50254	412	.49	.31	.62	3.8	.13	.41	.15	.71	.78	=
	50265	413	.51	.33	.77	4.0	.15	.39	.18	.80	.84	.10
	50266	383	.52	.32	.78	3.7	.18	.41	.15	.87	.88	.11
Control 1 ml Normal Saline	50291	413	.51	.35	.39	4.1	.15	—	.20	.78	.83	.12
	50300	430	.49	.30	.35	3.6	.28	.39	.15	.79	.82	.16
	50316	389	.54	.32	.31	4.0	.28	.45	.18	.76	.50	.16
	50317	402	.50	.28	.40	4.3	.12	.47	.18	.82	.96	.12

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N37255.06

DUP050041328