

34-PP

TIMA Inc.

CONTAINS NO CBI

June 16, 1992

FYI-OTS-0692-0854 INITIAL
SEQUENCE A

Document Control Officer
Chemical Information Division
Office of Toxic Substances (WH-557)
Environmental Protection Agency
401 M Street, SW
Washington, DC 20460



RE: "FYI" Update on Slag Wool Research - 18 Month Results

To Whom It May Concern:

A preliminary draft report (enclosed) was recently received by the Thermal Insulation Manufacturers Association (TIMA, Inc.) from the ongoing Chronic Multidose Oncogenicity Study of Mineral Wool Fibers in rats (Project No. 272024) at Research Consulting Company (RCC) in Geneva, Switzerland. A brief summary of the RCC results are indicated below in Table 1. Reports from two reviewing pathologists have also been received, and are also enclosed.

Pursuant to Section 8 of the Toxic Substances Control Act, 15 U.S.C. Sec. 2607 and EPA's interpretation of that provision, we are providing these reports from the 18-month sacrifice from this Study on an "FYI" basis. As the status report is the result of a preliminary evaluation of an ongoing study, the results presented herein should not be regarded as final. Any review should take into account the fact that the report is based upon incomplete information.

In October of 1990, a two-year rat inhalation study to determine the chronic effects of two different compositions of mineral wool fibers was initiated at RCC's laboratory in Geneva. Groups of rats were exposed in "nose-only" chambers for 6 hours per day, 5 days a week to 3, 16, or 30 mg/m³ of slag wool fiber (designated as MMVF 22 in the report). Another portion of the study exposed rats to rock wool fibers (MMVF 21); those results are the subject of a separate 8(e) filing. Negative controls (filtered air) and crocidolite asbestos exposed (10 mg/m³) animals were also included in the study.

The slag wool used in this study was presized to have an average diameter of approximately 1 μ and an average length of approximately 20 μ , so that the generated aerosol would be mostly rat respirable. (Approximately 2000 pounds of the product were used to obtain ten pounds of fiber for exposing the animals.) The dose levels of slag wool in the study equated to exposures of approximately 27, 123, and 210 f/cc respirable fibers. Human exposures are typically no greater than 1 f/cc.

After 3, 6, 12 and 18 months of exposure, 6 animals from each treatment group were sacrificed for interim pathological studies. The lungs were fixed in formalin, embedded in paraffin, sectioned, and stained for pathomorphological examination. All lungs were scored for pathological change according to the Wagner Scale (McConnell et al., 1984¹). The results are summarized below (See Table 1.)

RCC Table 1. Lung Histology Evaluation - Wagner Scores

Time	MMVF22 Concentration (mg/m ³)			Air Controls	Crocidolite*
	3	16	30		Asbestos 10 mg/m ³
3 Mo	2.0	2.5	2.5	1.0	4.0
6 Mo	2.0	2.7	3.0	1.0	4.2
12 Mo	2.5	2.3	3.0	1.0	4.0
18 Mo	2.2	2.5	2.8	1.0	4.2

* Exposure was terminated at 44 weeks due to toxic reaction (i.e. weight loss and death) of crocidolite-exposed animals.

After 3 months of exposure, a dose-dependent increase in cellularity (pulmonary change grades 2.0 and 2.5 on the Wagner Scale) was observed in all groups exposed to slag wool fibers. Those cellular changes are thought to be reversible and to occur to some extent when any particulate gains entrance into the deep lung. Fibrosis (Wagner Grade 4) was noted in the lung tissue samples taken from the six crocidolite-exposed animals. No lesions were observed in lung tissues taken from the 6 control animals, and these tissues received a Wagner Grade of 1.

Following 6 months of exposure, lung tissue samples obtained from slag wool exposed animals showed minimal progression of pulmonary alterations when compared to the 3-month observations. The low dose (3 mg/m³) group showed no progression from 3 to 6 months. The mid and high dose groups showed a small dose-dependent increase in reversible cellularity (pulmonary change grades 2.0 and 3.0 on the Wagner scale). Five of six lung tissue samples obtained from crocidolite-exposed animals were scored grade 4, and one sample was scored 5.

¹McConnell, E.E., Wagner, J.C., Skidmore, J.W., and Moore, J.A.
A comparative study of the fibrogenic and carcinogenic effects of UICC Canadian chrysotile B asbestos and glass microfibre (JM100). In "Biological Effects of Man-Made Mineral Fibers," Volume 2, World Health Organization, 1984.

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After 12 months of exposure, little or no progression of pulmonary alterations was observed in lung tissue samples obtained from slag wool exposed animals when compared to the 6 month Wagner scores (Table 1). All lung tissues obtained from the crocidolite-exposed (approximately 10 months exposure and 2 months recovery) rats received grade 4 scores, again indicating irreversible fibrosis. Lung tissues from air control animals were scored as Wagner Grade 1, indicating no lesions were observed.

Following 18 months of exposure, the lung tissues obtained from slag wool exposed animals showed little change from those from the 12 month sacrifice, suggesting that the reversible progressive pulmonary changes seen at 3 and 6 months had stopped. Lung tissues obtained from the crocidolite-exposed (approximately 10 months exposure and 8 months recovery) animals were scored Wagner Grade 4.2, and the tissues obtained from the 6 air control animals received Wagner Grade 1 scores.

The next scheduled sacrifice for this study will occur after 24 months of exposure (October 5, 1992). We will continue to provide your office with updates on new information from this study as we receive it from RCC. Should you wish to discuss the preliminary results of this study, please contact me at 203-324-7533.

Sincerely,

Frank J. Rauscher / cwf
Frank J. Rauscher, Jr., Ph.D.
Executive Director
TIMA, Inc.

PRELIMINARY DATA

SUBJECT TO CHANGE FOLLOWING
PATHOLOGY VERIFICATION AND AUDIT

CONTAINS NO CBI

TMA Inc.

PATHOLOGY REPORT (PRELIM. INFORMATION)
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TEST SYSTEM : RAT, ONCOGENICITY, INHALATION
SPONSOR : T.I.M.A., STAMFORD, CONN.

PATHOL. NO.: 92010 EJC
DATE : 30-MAY-92
FDS PATHDATA SYSTEM TM

SUMMARY

Pathomorphologic examination was performed on 189 male rats that were divided into 8 groups (groups 01 - 08, respectively). Except for group 02, each group consisted of 24 rats. Group 02 consisted of 21 rats. The rats were subjected to an inhalation oncogenicity study with Man-Made Vitreous Fibers (MMVF). The rats of group 01 served as the negative control and were exposed to filtered air. The rats of group 02 served as the positive control and were exposed to NIOSH Crocidolite at a dose level of 10 mg per cbm. The rats of groups 03, 04, and 05 were exposed to MMVF 21 at dose levels of 3, 16, and 30 mg/cbm, respectively. The rats of groups 06, 07, and 08 were exposed to MMVF 22 at dose levels of 3, 16, and 30 mg/cbm, respectively.

The rats were sacrificed according to the following schedule:

Sacrifice after Weeks of Exposure Recovery	Sacrifice Status	Group								
			01	02	03	04	05	06	07	08
13	Interim K1		6	6	6	6	6	6	6	6
26	Interim K2		6	6	6	6	6	6	6	6
44	2	Interim K3		3						
44	8	Interim K4		3						
44	32	Interim K5		3						
54		Interim K6	6		6	6	6	6	6	6
78		Interim K7	6		6	6	6	6	6	6
Intercurrent deaths			20	27	10	13	11	9	10	13

From all rats, nasal cavity, larynx, trachea, bronchi, lungs, mediastinal and mesenteric lymph nodes, liver, spleen, kidneys, heart, and all gross lesions were examined histologically.

Histologic changes were described according to distribution, severity, and morphologic character, and scored minimal, slight, moderate, marked, and massive.

In addition, in all rats sacrificed on schedule, the histologic grading system according to the criteria given by Wagner et al. (1974), was used (McCormell et al. 1984). In this grading system a grade 1.0 is considered normal, grades 2.0 and 3.0 are characterized by cellular changes (alveolar macrophages, bronchiolization, microgranulomas), and grades 4.0 to 8.0 represent the former lesions plus increasing distribution and degrees of fibrosis. The degree of fibrosis may range from minimal to moderate.

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but is consistent with grade 4.0 as long as no interlobular linking of the aforementioned lesions occurs. Grades 2.0 and 3.0 are considered potentially reversible, while grades 4.0 to 8.0 are thought to be non-reversible.

The cause of the intercurrent deaths was not determined.

Interim sacrifice after the 13-week exposure period (K1):

After 13 weeks of exposure to MMVF21, fiber-containing alveolar macrophages and microgranulomas at the bronchiolo-alveolar junction were noted in all dose groups. Alveolar bronchiolization was noted in 1 mid- and all high-dose rats. Collagen deposition at the bronchiolo-alveolar junction was noted in 3 high-dose rats. This was consistent with Wagner-grade 2 in the low-dose group, grade 2-3 in the mid-dose group, and grade 3-4 in the high-dose group.

After 13 weeks of exposure to MMVF22, fiber-containing alveolar macrophages were noted in all dose groups. Alveolar bronchiolization and microgranulomas at the bronchiolo-alveolar junction were noted in the mid- and high-dose groups. This was consistent with Wagner-grade 2 in the low-dose group, and grade 2-3 in the mid- and high-dose groups.

Interim sacrifice after the 26-week exposure period (K2):

After 26 weeks of exposure to MMVF21, fiber-containing alveolar macrophages and microgranulomas at the bronchiolo-alveolar junction were noted in all dose groups. Alveolar bronchiolization was noted in 5 mid- and all high-dose rats. Collagen deposition at the bronchiolo-alveolar junction was noted in 1 mid- and 4 high-dose rats. This was consistent with Wagner-grade 2 in the low-dose group, grade 2-3 in the mid-dose group, and grade 3-4 in the high-dose group.

After 26 weeks of exposure to MMVF22, fiber-containing alveolar macrophages were noted in all dose groups. Alveolar bronchiolization and microgranulomas at the bronchiolo-alveolar junction were noted in the mid- and high-dose groups. Minimal collagen deposition at the bronchiolo-alveolar junction was noted in 5 high-dose rats. This was consistent with Wagner-grade 2 in the low-dose group, grade 2-3 in the mid-dose group, and grade 3 in the high-dose group.

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SUMMARY

Adenoma:

1. Loss of pre-existing alveolar architecture
2. papillary formation into air spaces
3. Nuclear uniformity
4. May or may not be metaplasia to other cell types
5. Compression but no invasion of adjacent tissues.

Adenocarcinoma:

1. Expansion, compression, and invasion of adjacent tissues
2. Atypia - nuclear and/or cellular
3. Pleomorphism
4. Metastases
5. Metaplasia to other cell types is often present.

Mesothelial proliferation (hyperplasia):

1. Rounded enlarged mesothelial cells
2. Villous, papillary, or bud-like proliferation of single-layered mesothelial cells.

Mesothelioma:

1. Dysplastic, enlarged mesothelial cells sometimes showing vacuoles, karyomegaly, mitotic figures
2. Multilayered proliferation
3. Invasion
4. Sometimes sarcoma-like growth pattern.

After 78 weeks of study duration, non-neoplastic bronchiolar-alveolar hyperplasia was noted in 1 rat each exposed to filtered air, the low dose of MMVF 21, and the mid dose of MMVF22. An adenoma was noted in 1 rat each exposed to Crocidolite and the high dose of MMVF 22.

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METHODS

Group Design for Pathological Evaluation

Dose Group	Dose (mg/cbm)	Fibers	Number of Males
01	0	Neg. Control	24
02	10	NIEHS Crocidolite	21
03	3	MMVF 21	24
04	16	MMVF 21	24
05	30	MMVF 21	24
06	3	MMVF 22	24
07	16	MMVF 22	24
08	30	MMVF 22	24

These rats were sacrificed according to the following schedule:

Sacrifice after Weeks of Exposure Recovery	Sacrifice Status	Group							
		01	02	03	04	05	06	07	08
19	Interim K1	6	6	6	6	6	6	6	6
26	Interim K2	6	6	6	6	6	6	6	6
44	Interim K3		3						
44	Interim K4		3						
44	Interim K5		3						
54	Interim K6	6		6	6	6	6	6	6
78	Interim K7	6		6	6	6	6	6	6
Intercurrent deaths		20	27	10	15	11	9	10	13

Administration of the Test Article

The test article was administered by aerosol for 6 hours daily, excluding weekends.

Necropsy and Histopathology

The rats were anesthetized by intraperitoneal injection of pentobarbital and then killed by exsanguination.

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METHODS

Necropsy was performed on all rats. At postmortem examination, all organs were examined and all findings recorded.

Except for lungs and mediastinal lymph nodes, the tissues were fixed in 4% buffered formaldehyde solution. The lungs and mediastinal lymph nodes were fixed with Karnowski's fixative. The tissues were embedded in paraffin. Sections were cut at an approximate thickness of 4 micrometers and stained with hematoxylin and eosin. The lungs were also stained with Goldner's trichrome stain.

Sections of the following tissues from all rats killed on schedule were examined microscopically (number of sections per tissue):

Nasal cavity (4), trachea [incl. larynx] (1), lungs (2), lymph nodes [mediastinal, mesenteric] (2), liver (2), spleen (1), kidneys (2), heart (1), and all gross lesions.

Data Compilation

The animal data and macroscopic findings were transferred from RCC by magnetic discette into the PDS PATHDATA SYSTEM.

The microscopic findings were recorded by the undersigned pathologist using on-line input into the PDS PATHDATA SYSTEM.

All macroscopic and microscopic findings are given for each animal in text form under "Text of Gross and Microscopic Findings." The incidence of microscopic findings is also presented in tabular form. Incidence tables were created by computer.

The slides were evaluated in March 1991 (K1), April 1991 (K2), December 1991 (K3), May 1992 (K4, K5).

Histologic changes were described, wherever possible, according to distribution, severity, and morphologic character. Severity scores were assigned as given under "Explanation of Codes and Symbols."

In addition, the following histologic grading system for the classification of pulmonary changes related to the inhalation of fibers according to the criteria given by Wagner et al. (1974) was used. See table on next page.

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METHODS

Histologic Grading of Pulmonary Changes Related to Fiber Inhalation

- Cellular change: Normal 1 No lesion observed.
- Minimal 2 A few macrophages in the lumen of terminal bronchioles and alveoli.
- Mild 3 Presence of cuboidal epithelium lining the proximal alveoli (bronchiolization). No collagen, but reticulin fibers may be present in the interstitium at the bronchioalveolar junction. Luminal macrophages are more conspicuous, mononuclear cells may be found in the interstitium.
-
- Fibrosis: Minimal 4 Minimal collagen deposition at bronchioalveolar junction; increased bronchiolization; associated mucoid debris suggesting glandular pattern.
- Mild 5 Interlobular linking of lesion described in grade 4 and increased severity of fibrosis.
- Moderate 6 Early consolidation; parenchymal decrease.
- Severe 7 Marked fibrosis and consolidation.
- 8 Complete obstruction of most airways.

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METHODS

Pulmonary and pleural non-neoplastic and neoplastic proliferative lesions were classified according to the following criteria:

Bronchiolar-alveolar hyperplasia (BAH)

1. Retention of alveolar architecture
2. Air spaces are lined by cuboidal cells, mainly single-layered
3. Lack of cellular and nuclear atypia
4. Presence or absence of significant fibrosis

Adenoma

1. Loss of pre-existing alveolar architecture
2. Papillary formation into air spaces
3. Nuclear uniformity
4. May or may not be metaplasia to other cell types
5. Compression but no invasion of adjacent tissues.

Adenocarcinoma

1. Expansion, compression, and invasion of adjacent tissues
2. Nuclear and/or cellular atypia
3. Pleomorphism
4. Metastases
5. Metaplasia to other cell types is often present.

Mesothelial proliferation/hyperplasia

1. Rounded enlarged mesothelial cells
2. Villous, papillary or bud-like proliferation of single-layered mesothelial cells.

Mesothelioma

1. Dysplastic, enlarged mesothelial cells sometimes showing vacuoles, karyomegaly, mitotic figures
2. Multilayered proliferation
3. Invasion
4. Sometimes sarcoma-like growth pattern.

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RESULTS

Mortality

A total of 113 rats died or were killed in a moribund state during the first 78 weeks of the study: 20 in group 01, 27 in group 02, 10 in group 03, 15 in group 04, 11 in group 05, 9 in group 06, 10 in group 07, and 13 in group 08.

Gross and Microscopic Findings

Interim sacrifice after 13 weeks (K1)

Lungs:

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Areas of non-collapsed alveoli were noted in 3 rats each of groups 02 and 05, and 2 rats of group 08. Reddish foci were noted in 2 rats of group 01, and 1 rat each of groups 03, 05, and 08. Microscopically, Wagner-grade was noted in all rats of group 01.

In group 02, pulmonary change, grade 4 was noted in all rats. This change was characterized by alveolar macrophage aggregation, alveolar bronchiolization, microgranulomas and collagen deposition at the bronchiolo-alveolar junction.

In group 03, pulmonary change, grade 2 was noted in all rats. This finding was characterized by fiber-containing alveolar macrophages. In addition, microgranulomas were noted at the bronchiolo-alveolar junction.

In group 04, pulmonary change, grade 2 was noted in 5 rats, and grade 3 was noted in 1 rat. The grade 2 was characterized by fiber-containing alveolar macrophages. The grade 3 was characterized by alveolar bronchiolization. In addition, microgranulomas at the bronchiolo-alveolar junction were noted in 4 rats.

In group 05, pulmonary change, grade 3 was noted in 5 rats, and grade 4 was noted in 1 rat. The grade 3 was characterized by fiber-containing alveolar macrophages and alveolar bronchiolization. Slight collagen deposition at the bronchiolo-alveolar junction was noted in the rat with pulmonary change, grade 4. In 2 other rats, collagen deposition was also noted. Since this collagen deposition was only focal and minimal, the pulmonary change was still graded 3. Microgranulomas at the bronchiolo-alveolar junction were noted in all rats.

In group 06, pulmonary change, grade 2 was noted in all rats. This find-

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was characterized by fiber-containing alveolar macrophages.

In group 07, pulmonary change, grades 2 and 3 were noted in 3 rats each. These findings were characterized by fiber-containing alveolar macrophages in the rats with grade 2, and alveolar bronchiolization in those with grade 3. Microgranulomas at the bronchiolo-alveolar junction were noted in 4 rats.

In group 08, pulmonary change, grades 2 and 3 were noted in 3 rats each. These findings were characterized by fiber-containing alveolar macrophages in the rats with grade 2, and alveolar bronchiolization in those with grade 3. Microgranulomas at the bronchiolo-alveolar junction were noted in all rats.

Pleura:

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Focal mesothelial proliferation was noted in 1 rat of group 04, 4 rats of group 07, and 2 rats of group 08.

Other organs/tissues:

.....
A few lesions were noted which were not considered to distinguish exposed rats from controls.

Interim sacrifice after 26 weeks (K2)

Lungs:

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Areas of non-collapsed alveoli were noted in all rats of group 02, 4 rats of group 04, and 3 rats of group 05. Discolored and/or vitreous foci were noted in 4 rats of group 01, 1 rat each of groups 02, 04, and 07, 2 rats each of groups 03, 05, and 08, and 3 rats of group 06. The lungs were incompletely collapsed in all rats of group 02. Microscopically, Wagner-grade 1 was noted in all rats of group 01.

In group 02, pulmonary change, grade 4 was noted in 3 rats, and grade 5 was noted in 1 rat. This change was characterized by alveolar macrophage aggregation, alveolar bronchiolization, microgranulomas and collagen deposition at the bronchiolo-alveolar junction. In addition, the grade 5 was characterized by interlobular linking of the aforementioned lesions.

In group 03, pulmonary change, grade 2 was noted in all rats. This finding was characterized by fiber-containing alveolar macrophages. In addition, microgranulomas were noted at the bronchiolo-alveolar junction in

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1 rat.

In group 04, pulmonary change, grade 2 was noted in 1 rat, and grade 3 was noted in 5 rats. The grade 2 was characterized by fiber-containing alveolar macrophages. In addition, the grade 3 was characterized by alveolar bronchiolization. In addition, microgranulomas at the bronchiole-alveolar junction were noted in 4 rats.

In group 05, pulmonary change, grade 3 was noted in 4 rats, and grade 4 was noted in 2 rats. The grade 3 was characterized by fiber-containing alveolar macrophages and alveolar bronchiolization. Minimal to slight collagen deposition at the bronchiole-alveolar junction was noted in the rats with pulmonary change, grade 4. In 1 other rat, collagen deposition was also noted. Since this collagen deposition was only focal and minimal, the pulmonary change was still graded 3. Microgranulomas at the bronchiole-alveolar junction were noted in all rats.

In group 06, pulmonary change, grade 2 was noted in all rats. This finding was characterized by fiber-containing alveolar macrophages.

In group 07, pulmonary change, grade 2 was noted in 2 rats, and grade 3 was noted in 4 rats. Grade 2 was characterized by fiber-containing alveolar macrophages. In addition, grade 3 was characterized by alveolar bronchiolization. Microgranulomas at the bronchiole-alveolar junction were noted in 4 rats.

In group 08, pulmonary change, grade 3 was noted in all rats. This finding was characterized by fiber-containing alveolar macrophages and alveolar bronchiolization. Microgranulomas at the bronchiole-alveolar junction were noted in all rats.

Pleura:

.....
Focal pleural collagen deposition was noted in 3 rats each of groups 02, 03, and 07, 4 rats each of groups 04 and 08, 5 rats of group 05, and 2 rats of group 06.

Focal mesothelial proliferation was noted in 1 rat each of groups 02, 03, 04, and 06, and 2 rats of group 05.

Interstitial:

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Interstitial collagen deposition was noted in all rats of group 02.

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RESULTS

Other organs/tissues:

.....
A few lesions were noted which were not considered to distinguish exposed rats from controls.

In group 01, pulmonary change, grade 1 was noted in all rats.

Interim sacrifice after 54 weeks (K4)

Lungs:

.....
Areas of non-collapsed alveoli were noted in all rats of groups 02 and 05, and 4 rats of group 04. Discolored and/or vitreous foci were noted in 2 rats each of groups 01 and 03, 5 rats of group 02, and 1 rat each of groups 05, 06, and 07. The lungs were incompletely or not collapsed in all rats of group 02, 5 rats of group 04, and 3 rats of group 05. Microscopically, Wagner-grade 1 was noted in all rats of group 01.

In group 02, pulmonary change, grade 4 was noted in all rats. This change was characterized by alveolar macrophage aggregation, alveolar bronchiolization, microgranulomas and collagen deposition at the bronchiole-alveolar junction.

In group 03, pulmonary change, grade 2 was noted in all rats. This finding was characterized by fiber-containing alveolar macrophages. Focal bronchiolar-alveolar hyperplasia was noted in 1 rat.

In group 04, pulmonary change, grade 2 was noted in 1 rat, and grade 3 was noted in 5 rats. The grade 2 was characterized by fiber-containing alveolar macrophages. In addition, the grade 3 was characterized by alveolar bronchiolization. Microgranulomas at the bronchiole-alveolar junction were noted in all rats, and minimal focal collagen deposition was noted in 3 rats.

In group 05, pulmonary change, grade 3 was noted in 4 rats, and grade 4 was noted in 2 rats. The grade 3 was characterized by fiber-containing alveolar macrophages and alveolar bronchiolization. Minimal to slight collagen deposition at the bronchiole-alveolar junction was noted in the rats with pulmonary change, grade 4. In 3 other rats, collagen deposition was also noted. Since this collagen deposition was only focal and minimal, the pulmonary change was still graded 3. Microgranulomas at the bronchiole-alveolar junction were noted in all rats.

In group 06, pulmonary change, grades 2 and 3 were noted in 3 rats each. The grade 2 was characterized by fiber-containing alveolar macrophages.

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In addition, the grade 3 was characterized by alveolar bronchiolization.

In group 07, pulmonary change, grade 2 was noted in 1 rat, and grade 3 was noted in 5 rats. Grade 2 was characterized by fiber-containing alveolar macrophages. In addition, grade 3 was characterized by alveolar bronchiolization. Microgranulomas at the bronchiole-alveolar junction were noted in 5 rats.

In group 08, pulmonary change, grade 3 was noted in all rats. This finding was characterized by fiber-containing alveolar macrophages and alveolar bronchiolization. Microgranulomas at the bronchiole-alveolar junction were noted in all rats, and minimal focal collagen deposition was noted in 3 rats.

Pleura:

Focal pleural collagen deposition was noted in 5 rats of group 02, 1 rat of group 03, 3 rats of group 04, and 2 rats of group 04.

Interstitium:

Interstitial collagen deposition was noted in 5 rats each of groups 02 and 04, all rats of group 05, 1 rat each of groups 06 and 07, and 2 rats of group 08.

Mediastinal lymph nodes:

Fibers in macrophages were noted in 5 rats of group 07 and all rats of group 08.

Other organs/tissues:

A few lesions were noted which were not considered to distinguish exposed rats from controls.

Interim sacrifice after 78 weeks (K5)

Lungs:

Areas of non-collapsed alveoli were noted in 1 rat of group 02, 4 rats of group 04, all rats of group 05, and 1 rat each of groups 07 and 08. Discolored and/or vitreous foci were noted in 2 rats of group 01, 3 rats of group 02, 1 rat of group 03, 3 rats of group 05, and 1 rat of group 06. The lungs were incompletely or not collapsed in all rats of group 02

PATHOLOGY REPORT (PRELIM. INFORMATION) PAGE PAT: 15/ 57
 PRINCIPAL SECTION RCC NO.: 272024

 TEST ARTICLE : MMVF 21 AND 22 PATHOL. NO.: 92010 HJC
 TEST SYSTEM : RAT, ONCOGENICITY, INHALATION DATE : 25-MAY-92
 SPONSOR : T.I.M.A., STAMFORD, CONN. PDS PATHDATA SYSTEM TM

RESULTS

and 1 rat of group 05. Gray-white nodules were noted in 1 rat each of groups 03, 07, and 08. Microscopically, Wagner-grade 1 was noted in all rats of group 01.

In group 02, pulmonary change, grade 4 was noted in 5 rats, and grade 5 was noted in 1 rat. These changes were characterized by alveolar macrophage aggregation, alveolar bronchiolization, microgranulomas and collagen deposition at the bronchiolo-alveolar junction. Grade 5 was characterized by interlobular linking of the aforementioned lesions.

In group 03, pulmonary change, grade 2 was noted in 3 rats, and grade 3 was noted in 3 rats. These findings were characterized by fiber-containing alveolar macrophages in all rats and alveolar bronchiolization in 3 rats. Microgranulomas were noted in 1 rat.

In group 04, pulmonary change, grade 3 was noted all rats. This finding was characterized by fiber-containing alveolar macrophages and alveolar bronchiolization. Microgranulomas and minimal collagen deposition at the bronchiolo-alveolar junction were noted in all rats.

In group 05, pulmonary change, grade 3 was noted in all rats. This finding was characterized by fiber-containing alveolar macrophages and alveolar bronchiolization. Minimal to slight collagen deposition at the bronchiolo-alveolar junction was noted in all rats. Microgranulomas at the bronchiolo-alveolar junction were noted in all rats.

In group 06, Wagner-grade 1 was noted in 1 rat, pulmonary change, grade 2 was noted in 3 rats, and grade 3 was noted in 2 rats. The grade 2 was characterized by fiber-containing alveolar macrophages. In addition, the grade 3 was characterized by alveolar bronchiolization.

In group 07, pulmonary change, grades 2 and 3 were noted in 3 rats each. Grade 2 was characterized by fiber-containing alveolar macrophages. In addition, grade 3 was characterized by alveolar bronchiolization. Microgranulomas at the bronchiolo-alveolar junction were noted in 2 rats.

In group 08, pulmonary change, grade 2 was noted in 1 rat, and grade 3 was noted in 5 rats. Grade 2 was characterized by fiber-containing macrophages. In addition, grade 3 was characterized by alveolar bronchiolization. Microgranulomas at the bronchiolo-alveolar junction were noted in all rats, and minimal focal collagen deposition was noted in 4 rats.

PRELIMINARY DATA
SUBJECT TO CHANGE FOLLOWING
PATHOLOGY VERIFICATION AND AUDIT

TIMA Inc.

PATHOLOGY REPORT (PRELIM. INFORMATION)
 PRINCIPAL SECTION

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PAT: 16/ 57
 NO.: 272024

TEST ARTICLE : MMVF 21 AND 22
 TEST SYSTEM : RAT, ONCOGENICITY, INHALATION
 SPONSOR : T.I.M.A., STAMFORD, CONN.

PATHOL. NO.: 92010 HJC
 DATE : 30-MAY-92
 PDS PATHDATA SYSTEM TM

RESULTS

Pleura:

.....
 Focal pleural collagen deposition was noted in 1 rat each of groups 01, 02, and 06. 2 rats of group 03, and 3 rats of group 05. Mesothelial proliferation was noted in 1 rat of group 03.

Interstitial:

.....
 Interstitial collagen deposition was noted in 3 rats each of groups 02 and 08, all rats of groups 04 and 05, and 1 rat of group 07.

Non-neoplastic bronchiolar-alveolar hyperplasia was noted in 1 rat each of groups 01, 03, and 07 (nos. 100, 398, 938).

Bronchiolar-alveolar adenomas were noted in 1 rat each of groups 02 and 08 (nos. 211, 1084).

PATHOLOGY REPORT (PRELIM. INFORMATION)
PRINCIPAL SECTIONPAGE PAT: 17/ 57
RCC NO.: 272024

TEST ARTICLE	: MMVF 21 AND 22	PATHOL. NO.:	92010 HJC
TEST SYSTEM	: RAT, ONCOGENICITY, INHALATION	DATE	: 25-MAY-92
SPONSOR	: T.I.M.A., STAMFORD, CONN.	PDS PATHDATA SYSTEM	TM

CONCLUSIONS

At all given time points, a dose-relationship of the severity of pulmonary alterations in the rats exposed to MMVF 21 and MMVF 22 was noted.

At all given time points, the severity of pulmonary alterations is considered to be more pronounced in the rats exposed to MMVF 21 than in those exposed to MMVF 22.

Between the interim sacrifice intervals of 13 and 26 weeks, the severity of pulmonary alterations is considered to be minimally increased in the groups exposed to 16 and 30 mg/cbm MMVF 21 and 22 (mid- and high-dose). This increase is considered to represent a minimal progression of the pulmonary alterations. A slight progression of pulmonary change was noted between 54 and 78 weeks in the rats exposed to MMVF 21, whereas no progression of pulmonary change was noted between the intervals of 26 and 54 weeks, and 54 and 78 weeks in the rats exposed to MMVF 22.

06-05-92 11:21 AM FROM USG CORP

P01

JUN 5 '92 10:14 FROM TMA

TO MUSSELMAN

PAGE.007

PRELIMINARY DATA
SUBJECT TO CHANGE FOLLOWING
PATHOLOGY VERIFICATION AND AUDIT

TMA Inc.

PATHOLOGY REPORT (FOLLOW-UP INFORMATION)

PAGE: 19 / 57
NO. : 272024

TEST ARTICLE : MCVF 21 AND 22
TEST SYSTEM : RAT, ORODUODENICITY, INHALATION
SPONSOR : T.I.M.A., STAMFORD, CONN.

PATROL. NO.: 98010 HJC
DATE : 16-MAY-92
FDC PATHDATA SYSTEM IN

SUMMARY OF SELECTED FINDINGS DIAGNOSED AT THE DIFFERENT TIME INTERVALS

Table 1: Pulmonary changes

Group Fiber Type	Dose (mg/cbm)	Exposure (weeks)	Number of rats with pulmonary changes, grade *				
			1	2	3	4	5
01 Control	0	13	0	0	0	0	0
		26	0	0	0	0	
		34	0	0	0	0	
		78	0	0	0	0	
02 Crocid.	10	13	0	0	0	0	0
		26	0	0	0	0	1
		34	0	0	0	0	1
		78	0	0	0	0	1
03 MCVF 21	3	13	0	0	0	0	0
		26	0	0	0	0	0
		34	0	0	0	0	0
		78	0	0	0	0	0
04 MCVF 21	16	13	0	0	0	0	0
		26	0	0	0	0	0
		34	0	0	0	0	0
		78	0	0	0	0	0
05 MCVF 21	30	13	0	0	0	0	0
		26	0	0	0	0	0
		34	0	0	0	0	0
		78	0	0	0	0	0

971 St. Mather Drive
Chappa, N. 06034-1205
Tel: 617-552-1111

TO: Name: John H. Kelly
Firm: OSF
FAX Number: 617-557-7524
FROM: Name: ASD
Number of Pages: 10 Date: 06-05-92

If you do not receive all pages, please call (617) 600-4300

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TO MUSSELMAN

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PRELIMINARY DATA
SUBJECT TO CHANGE FOLLOWING
PATHOLOGY VERIFICATION AND AUDIT
TIMA INC.

PATHOLOGY REPORT (PRELIM. INFORMATION)

PAGE
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PAT: 10/ 57
NO.: 272024

TEST ARTICLE : MCVT 21 AND 22
TEST SYSTEM : RAT, CROSSSENSITIVITY, INHALATION
SPONSOR : F.I.N.A., STAMFORD, CONN.

PATHOL. NO.: 22018 EJC
DATE : 30-MAY-92
PDS PATHDATA SYSTEM TM

SUMMARY OF SELECTED FINDINGS DIAGNOSED AT THE DIFFERENT TIME INTERVALS

Table I - cont'd.

06	5	18		0		
MCVT 22		26		0		
		34		3	3	
		78	1	3	3	
07	16	15		3	3	
MCVT 22		26		2	4	
		34		5	1	
		78		3	3	
08	30	19		3	3	
MCVT 22		26		3	4	
		34		1	0	
		78		1	5	

* Grading system given by Wagner et al. (1974)

1/2

Ernest E. McConnell, D.V.M., M.S.
Consultant in Toxicology and Pathology

Office Telephone
(919) 848-1576

3028 Ethan Lane
Laurdane Est.
Raleigh, NC 27613

CONTAINS NO CBI

May 28, 1992

To: Dr. Frank J. Rauscher
TIMA
29 Bank St.
Stamford, CT 06901

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JUN - 2 1992

FJR AK TIMA _____

From: Dr. McConnell

Subject: Mineral Wool Rat Study - 18 Month Pathology Review

Following is my interpretation of the pathology (slides) from the 18 month sacrifice of the rats in the RCC Rock (RCC #21) and Slag wool (RCC #22) multidose studies.

CHAMBER CONTROLS - (Animal #95, 96, 97, 98, 100 and 102) - The negative control animals show no lesions. There is no concurrent pulmonary disease. The rats in this group qualify as Wagner grade 1.

POSITIVE CONTROLS (CROCIDOLITE) - (Animal #250, 251 and 252) - The rats in this group are fairly uniform in their response. A minimal amount of macrophage infiltration in the area of the terminal bronchioles and proximal alveoli was observed; of approximate severity to that observed at 12 months. A moderate degree of bronchiolization was clearly evident in these same areas and may have been more severe than at 12 months. Typical microgranulomas and a number of larger granulomas containing a significant amount of collagen (fibrogranulomas) were observed. A moderate amount of well defined fibrosis was present in the walls of the proximal alveoli. It appeared to be more condensed (mature) than at 12 months and in one rat I observed a fair amount of interlobular linking of the collagen (Grade 5). Overall, the above lesions were a little more severe than those observed at 12 months and were consistent with an average Wagner grade 4.5. Definitive focal pleural fibrosis (minimal) was observed in the pleura of 1 of 3 rats.

ROCK WOOL, 3 mg/m³ - (Animal #378, 379, 380, 381, 382 and 384) - Occasional macrophages containing fibers were observed but the number was not much above the background level. One rat showed a few microgranulomas in the walls of the proximal alveoli. There was no progression from 12 months. The lungs from these rats would be classified as Wagner grade 1.5. No fiber related lesions were observed in the pleura.

ROCK WOOL, 16 mg/m³ - (Animal #519, 520, 521, 522, 523 and 524) -

23

There is a mild amount of macrophage infiltration (some in clumps) in the area of the terminal bronchioles and proximal alveoli, some of which contained an occasional fibers. Variable numbers of microgranulomas were also observed. A minimal amount of bronchiolization was observed in all 6 rats. There was clear evidence of early fibrosis in the walls of the proximal alveoli in 4 of 6 rats and was suspected in another. The overall lesion averaged Wagner grade 3.8, although 4 of the animals would have to be classified as grade 4.0. This represents a distinct progression from the 12 month time point. No treatment related lesions were observed in the pleura.

ROCK WOOL, 30 mg/m³ - (Animal #658, 660, 661, 662, 663 and 664) - The lesions are clearly more apparent than in the 16 mg/m³ exposed animals. In addition to increased numbers of macrophages and microgranulomas an increased amount of bronchiolization was observed. Fibers were easily identified within the macrophages and microgranulomas. All six rats showed a minimal to mild amount of fibrosis in the walls of the proximal alveoli. The overall lesion averaged Wagner grade 4.2, which shows that there was some progression from the 12 month time point. Two of 6 rats showed a minimal amount of focal pleural fibrosis but I am not sure that it is treatment related because similar lesions are occasionally observed in control rats of this age.

SLAG WOOL, 3 mg/m³ - (Animal #799, 800, 801, 802, 803 and 804) - Although there were a few alveolar macrophages, most of which contained fibers, it was difficult to differentiate the lungs from the controls. There was no progression from the 12 month time point. The average was Wagner grade 1.2.

SLAG WOOL, 16 mg/m³ - (Animal #938, 939, 940, 941, 942 and 944) - I felt that there was a minimal increase in the number of macrophages in 5 of 6 rats. Most of the macrophages contained fibers. There was no progression from 12 months. Overall, the lesion averaged Wagner grade 1.5. One rat (#938) showed a focal area of bronchoalveolar hyperplasia (BAH). No treatment related lesions were observed in the pleura.

SLAG WOOL, 30 mg/m³ - (Animal #1079, 1080, 1081, 1082, 1083 and 1084) - All rats in this group showed a minimal increase in the number of pulmonary macrophages, which were concentrated in the area of the terminal bronchioles and proximal alveoli, although there was no increase from the 12 month time point. Fibers were clearly evident in most of the macrophages. An occasional microgranuloma was observed. Fibers/fragments were observed in the peribronchial lymphoid tissue. The overall lesion averaged Wagner grade 1.7 which shows that there has not been demonstrable progression from the 12 month time point. One rat (#1084) showed a focal area of BAH. No lesions were observed in the pleura.

HE

SUMMARY - There appeared to be a definite dose response with both types of fibers, but especially with the rock. Additionally, it is now clear that the rock fiber causes significantly more of a pulmonary response than the slag fiber. The of these lesions can only be determined after further exposure; I do not think it would be appropriate to predict what will happen at this time.

If you have questions please let me know.

Sincerely,

Ernest E. McConnell

25

- 0 - No lesion
- 1 - Minimal
- 2 - Mild
- 3 - Moderate
- 4 - Marked

SUMMARY PATHOLOGY REPORT

STUDY - RAT MMVF #21 (Rock Wool)

DATE - May 28, 1992

GROUP	MACROPHAGE	BRONC	FIBROSIS	GRADE	PLEURA	OTHER
<u>3 Month</u>						
Control	0	0	0	1.0	0	
3 mg/m ³	0	0	0	1.0	0	
16 mg/m ³	1	0	0	1.8	0	Macrophages with fibers. A few microgranulomas.
30 mg/m ³	1.5	0	0	2.0	0	More fibers and microgranulomas.
<u>6 Month</u>						
Control	0	0	0	1	0	
3 mg/m ³	0.8	0	0	1.5	0	A few fibers in macrophages
16 mg/m ³	1.0	0.6	0	2.3	0	More fibers; giant cells and microgranulomas
30 mg/m ³	1.5	1.0	0	2.6	0	More fibers and microgranulomas & giant cells.

26

- 0 - No lesion
- 1 - Minimal
- 2 - Mild
- 3 - Moderate
- 4 - Marked

HISTOPATHOLOGY

STUDY - RAT MMVF #21 (Rock Wool) Cont'd.

DATE - May 28, 1992

GROUP	MACROPHAGE	BRONC	FIBROSIS	GRADE	PLEURA	OTHER
-------	------------	-------	----------	-------	--------	-------

12 Month

Control	0	0	0	1.0	0	
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3 mg/m ³	0.3	1.0	0	1.3	0	A few fibers in macrophages.
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16 mg/m ³	1.3	1.1	0	2.4	0	Macrophages with fibers. Also in lymph nodes. Microgran.
----------------------	-----	-----	---	-----	---	--

30 mg/m ³	1.9	2.0	0.2	3.5	0	More of same. Early fibrosis in 2/6 animals.
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18 Month

Control	0	0	0	1.0	0	
---------	---	---	---	-----	---	--

3 mg/m ³	0.3	0	0	1.2	0	A few fibers in macrophages.
---------------------	-----	---	---	-----	---	------------------------------

16 mg/m ³	1.7	1.1	0.8	3.8	0	Fibers in macrophages. Early fibrosis in 4/6 rats.
----------------------	-----	-----	-----	-----	---	--

30 mg/m ³	2.0	1.7	1.3	4.1	0.2	Fibers in macrophages. Fibrosis in 6/6 rats.
----------------------	-----	-----	-----	-----	-----	--

22

- 0 - No lesion
- 1 - Minimal
- 2 - Mild
- 3 - Moderate
- 4 - Marked

SUMMARY PATHOLOGY REPORT

STUDY - RAT MMVF #22 (Slag wool)

DATE - May 28, 1992

GROUP	MACROPHAGE	BRONC	FIBROSIS	GRADE	PLEURA	OTHER
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3 Month

Control	0	0	0	1.0	0	
---------	---	---	---	-----	---	--

3 mg/m ³	0	0	0	1.0	0	
---------------------	---	---	---	-----	---	--

16 mg/m ³	0.3	0	0	1.2	0	A few fibers in macrophages.
----------------------	-----	---	---	-----	---	------------------------------

30 mg/m ³	1.0	0	0	2.0	0	More macrophages and a few microgranulomas.
----------------------	-----	---	---	-----	---	---

6 Month

Control	0	0	0	1.0	0	
---------	---	---	---	-----	---	--

3 mg/m ³	0.3	0	0	1.3	0	A few fibers in macrophages.
---------------------	-----	---	---	-----	---	------------------------------

16 mg/m ³	0.8	0	0	1.8	0	More macrophages and a few giant cells.
----------------------	-----	---	---	-----	---	---

30 mg/m ³	1.0	0	0	2.0	0	More of the above.
----------------------	-----	---	---	-----	---	--------------------

80

- 0 - No lesion
- 1 - Minimal
- 2 - Mild
- 3 - Moderate
- 4 - Marked

HISTOPATHOLOGY

STUDY - RAT MMVF #22 (Slag Wool) Cont'd.

DATE - May 28, 1992

GROUP	MACROPHAGE	BRONC	FIBROSIS	GRADE	PLEURA	OTHER
<u>12 Month</u>						
Control	0	0	0	1.0	0	
3 mg/m ³	0.3	0	0	1.3	0	
16 mg/m ³	1.0	0	0	1.5	0	A few macrophages containing fibers.
30 mg/m ³	1.5	0	0	2.0	0	A few macrophages containing fibers.
<u>18 Month</u>						
Control	0	0	0	1.0	0	
3 mg/m ³	0.2	0	0	1.2	0	
16 mg/m ³	0.8	0	0	1.4	0	BAH - 1/6 A few macrophages containing fibers.
30 mg/m ³	0.9	0	0	1.6	0	BAH - 1/6 A few macrophages containing fibers.

29

- 0 - No lesion
- 1 - Minimal
- 2 - Mild
- 3 - Moderate
- 4 - Marked

SUMMARY PATHOLOGY REPORT
 STUDY - CROCIDOLITE ASBESTOS
 DATE - May 28, 1992

GROUP MACROPHAGE BRONC FIBROSIS GRADE PLEURA OTHER

3 Month

GROUP	MACROPHAGE	BRONC	FIBROSIS	GRADE	PLEURA	OTHER
Control	0	0	0	1.0	0	
10 mg/m ³	2.0	2.0	2.0	4.0	0	Many macrophages & microgranulomas.

6 Month

GROUP	MACROPHAGE	BRONC	FIBROSIS	GRADE	PLEURA	OTHER
Control	0	0	0	1.0	0	
10 mg/m ³	2.0	2.5	2.0	4.0	0	Fibrosis is more developed.

12 Month

GROUP	MACROPHAGE	BRONC	FIBROSIS	GRADE	PLEURA	OTHER
Control	0	0	0	1.0	0	
10 mg/m ³	1.1	2.5	3.0	4.2	1.0	Mature fibrosis. Pleural fibrosis in 3/6 rats.

30

- 0 - No lesion
- 1 - Minimal
- 2 - Mild
- 3 - Moderate
- 4 - Marked

SUMMARY PATHOLOGY REPORT

STUDY - CROCIDOLITE ASBESTOS (Cont'd)

DATE - May 28, 1992

GROUP MACROPHAGE BRONC. FIBROSIS GRADE PLEURA MISC.

18 Month

Control 0 0 0 1.0 0

10 mg/m³ 1.3 3.0 2.7 4.5 0.3

PAUL KOTIN, M.D.
4505 S. Yosemite #339
Denver, Colorado 80237
(303) 770-6882

1 June 1992

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JUN - 5 1992

FJR RAUSCHER TIMA EEF

Frank J. Rauscher, Jr., Ph.D.
Executive Director
TIMA, Inc.
29 Bank Street
Stamford, CT 06901

RAUSCHER
C: TIMA
6-5-92
done via c.

Dear Dr. Rauscher:

In accordance with your request I have reviewed the histologic sections from the 18 month sacrifice of rats from TCC (Geneva) project 272204--inhalation carcinogenesis study MMVF #21 and MMVF #22.

Pathology Report

The lung sections were prepared in accordance with standard protocol and were stained the H and E and with Masson Trichrome. Six rats from each of the 3 dose levels were sacrificed as were 6 from the negative control group and crocidolite.

Group 1 --Chamber Controls (Rats #95,96,97,99,100,102)

No changes were observed other than those attributable to the aging process.

Wagner Grade 1

Group 2 -- Positive Controls (Crocidolite) 10 mgm/cu.met.
(Rats#250,251,252)

Minimal progression has accrued since the 12 month sacrifice. Macrophage infiltration remains at a constant level when compared to the 12 month findings. Focal areas of interstitial fibrosis can be noted with slight increase in intensity and diffuseness. Foci of pleural thickening, chiefly due to fibrosis rather than cellular proliferation or hyperplasia is somewhat more prominent.

Wagner Grade 5

MMVF #21

Group 3 --Rockwool 3mg/cu.met.=25f/cc.
(Rats # 378,379,380,381,382,384)

There is clear evidence of progression of the pulmonary response when compared with the 12 month findings. The parenchyma shows numerous foci of fibrotic nodular thickening in the peribronchiolar and alveolar duct areas. These areas vary in the ratio of fibrosis to cellularity. The fibrosis in one or two areas suggests involvement of the interstitium, though this is not

conclusive at this time. The pleura shows multiple foci of pleural thickening, primarily fibrotic with some evidence of cellular stimulation.

Wagner Grade 3.5

Group 4 --Rockwool 16 mg/cu.met. (150f/cc)
(Rats #519, 520, 521, 522, 523, 524)

Progression at this level since the 12 month sacrifice has been vigorous. The parenchyma shows numerous foci of microgranuloma formation. Fibrous nodules and fibrous caps over the epithelium in the peribronchiolar, alveolar duct, and proximal alveoli are prominent. The aveolar duct and septa show early but clear findings of interstitial fibrosis. Pleural thickening can be seen in multiple areas with both collagen deposition and cellular hyperactivity.

Wagner Grade 4

Group 5 --Rockwool 30mg/cu.met. (300f/cc)
(Rats # 658, 660, 661, 662, 663, 664)

The findings described in the lungs of rats from Group 4 are slightly more prominent in this high dose group. Parenchymal and pleural changes are consistent with continuing progression as there is little evidence of stabilization of findings. When compared with the lungs at the 12 month sacrifice all elements, (macrophage presence, fibrosis, focal and interstitial and pleural changes) are advanced in intensity and areas of involvement. Interlobular linking has not occurred to any degree, nevertheless I do believe the fibrosis merits a grading of Wagner 5 because of the frequent involvement of the fibrotic process beyond the alveolar ducts and proximal alveoli to the entire alveolar unit.

Wagner Grade 5

Group 6 -- Slagwool 3 mgm/cu.met. (25f/cc)
(Rats #799, 800, 801, 802, 803, 804)

Progression has been minimal if in fact at all real. I am impressed with the absence of any major change since the 12 month sacrifice. No evidence of fibrosis is discernable, the macrophage infiltration may be somewhat increased.

Wagner Grade 2

Group 7 -- Slagwool 16mg/cu.met. (150f/cc)
(Rats #938, 939, 940, 941, 942, 944)

Evidence of progression, though of a low level, is clearly present. Microgranuloma and focal fibrosis in the peribronchiolar area is occasionally observed, with little extension beyond the

alveolar duct to the alveolar septa. Bronchiolization in rat #938 is prominent in one area immediately underlying the pleura. Few foci of pleural thickening can be observed in 3 of the 6 rats.

Wagner Grade 3.5

Group 8 -- Slagwool 30mg/cu.met. (300f/cc)
(Rats #1079,1080,1081,1082,1083,1084).

Progression has been minimal but real. Microgranuloma formation is somewhat more diffuse, but extension of the fibrosis to the interstitium still cannot be observed. Macrophage presence is prominent and fibers continue to be "plentiful." Pleural changes have not progressed when compared with the 12 month sacrifice. A single rat, #1084, has florid bronchioloalveolar hyperplasia covering a relatively large area. I believe early adenoma formation describes one focus within the area.

Wagner Grade 3.75

Conclusions

1. The changes observed are consistent with an exposure-response pattern.
2. As in the past my Wagner grading is based on the most advanced lesions within each group. However, in contrast to earlier reports, the intragroup variation has narrowed.
3. The changes seen in rats exposed to Rockwool have now progressed from reversible to irreversible and at the higher dose levels I would predict continued progression. This in contrast to Slagwool where the parenchymal changes are still essentially within the reversible range, the very very early possible bronchioloalveolar adenoma notwithstanding.
4. What was an earlier impression is now, I believe, an established reality -- Rockwool is more potent than Slagwool in inducing parenchymal and pleural abnormalities.
5. Comparative responses are as follows:

MMVF#21 -- Wagner Grade

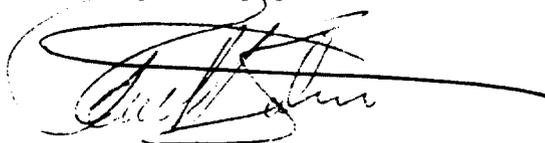
	<u>6 mos.</u>	<u>12 mos.</u>	<u>18mos</u>
Low Dose	2	2	3.5
Middle Dose	3	3	4
High Dose	4	4	5

34

MMVF #22 -- Wagner Grade

Low Dose	2	2	2
Middle Dose	3	3	3.5
High Dose	3.5	3.5	3.75

Very truly yours,



Paul Kotin M.D.