

8EHQ-0602-15157 MR 59524



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May 20, 2002

Via Certified Mail

Document Processing Center, Room 6428
Attn: Section 8(e) Coordinator
Office of Pollution Prevention and Toxic Substances
U.S. Environmental Protection Agency
EPA East Building
1201 Constitution Avenue, N.W.
Washington, DC 20004

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Re: Section 8(e) Notification of Substantial Risk for P98-1274/1275

Pursuant to receiving interim compilation of results from our contract laboratory on April 30, 2002, UOP is submitting the following Notification of Substantial Risk as required by Section 8(e) of the Toxic Substances Control Act (TSCA).

The attached summary is from a study that is being conducted in accordance with TSCA Section 5(e) Consent Order for P98-1275/P98-1275. Please note that this notification is based on preliminary data from an interim compilation of results generated following the 90-day exposure and 90-day recovery periods. Overall, conclusions on health risks associated with the test material can only be finalized following a thorough review of the interim findings.

We are in the process of scheduling a June meeting through the PMN Program Manager, which will include appropriate EPA technical personnel, to discuss the interim findings from this study.

Sincerely,

Michael L. Rataj, CIH
Manager, Health, Safety, and Environmental Skill Center
Phone: (847) 375-7570; Fax (847) 391-2953; e-mail: mlrataj@uop.com

cc: NJNedeau, MGreenwood, RAPalmer, Mary Begley, U.S. EPA, File: 5220

Attachments

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Original 1 of 2

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2nd Interim Compilation of Results
This is not an Official Interim Report

Final Report

**90-Day Inhalation Toxicity Study of
a Non-Fibrous Synthetic Zeolite Analog in the Rat
Fraunhofer ITA Study No. 02G01017**

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Managing Director: Prof. Dr. U. Heinrich

This report consists of 236 pages.

April 30, 2002

INFORMATION ON THE STUDY

Fraunhofer ITA Study No.: 02G01017

Test Facility: Fraunhofer ITA
Inhalation Room T1.030
Necropsy Room T1.07

Test Substance: Non-Fibrous Zeolite Analog
Reference Substances: Quartz DQ 12 (positive control)
Titanium Dioxide (negative control)

Fraunhofer ITA Study Director: Dr. O. Creutzenberg

Sponsor's Project Monitor: M.L. Rataj

Sponsor's Project Consultant: Prof. Dr. G. Oberdörster

Study Initiation Date: July 27, 2001

Experimental Start Date: July 30, 2001
(Start of animal exposure = first date the test substance is applied to the test system)

Experimental Termination Date: *will be filled in upon finalization*
(Last sacrifice = last date on which data are collected directly from the study)

Study Completion Date: *will be filled in upon finalization*

Conduct of Study

Good Laboratory Practice (GLP)

The study procedures and data comply with current Standard Operating Procedures and the Principles of Good Laboratory Practice (German Chemicals Law, Paragraph 19 a, Appendix 1, pp. 1724-1732, July 25, 1994), amended on May 14, 2001 and with regulations of the German Animal Protection Law (Tierschutzgesetz of May 25, 1998).

Deviations from the study plan

No deviations from the study plan were necessary.

Amendments to the study plan

Five amendments to the study plan were made (see Appendix XVII).

Study Staff

Laboratory Animal Veterinarians	Dr. med. vet. C. Dasenbrock	<i>will be filled in upon finalization</i>
	Dr. med. vet. Th. Tillmann	
Aerosol Scientist	Dr. rer. nat. G. Pohlmann	
Biochemist	Dr. rer. nat. O. Creutzenberg	
Hematologist/Clinical Chemist	Prof. Dr. rer. nat. W. Bartsch	
Inorganic Chemist	Dr. rer. nat. A. Preiss	
Histopathologist	Dr. med. vet. H. Ernst	
Biostatistician	Prof. Dr. H. Hecker	
Quality Assurance	Dr. M. Ketkar	

EXECUTIVE SUMMARY

- In a 90-day nose-only inhalation study rats were exposed to non-fibrous zeolite (0.45, 1.9 and 10 mg/m³), quartz DQ 12 (7.2 mg/m³) and titanium dioxide (6.3 mg/m³). Exposure duration was 6 hours/day, 5 days/week for 3 months. Animals were investigated after end of exposure and after a 3-month post-exposure observation period.
- In all groups effects indicating systemic toxicity were not observed.
- Hematological and blood clinical chemistry did not result in substance-related effects. The only significant findings were increased neutrophil and decreased lymphocyte levels in the zeolite high (females only) and DQ 12 groups indicating a local pulmonary inflammation.
- The desired equal lung retention of test substances in the three high dose groups was achieved (about 1100 µg in males and 1000 µg in females). Clearance of test substances in the post-exposure period was estimated. Clearance was unimpaired in the zeolite low and mid dose groups and very slightly retarded in the zeolite high and the TiO₂ group. However, particle clearance had collapsed in the DQ 12 group.
- Biochemical data in the bronchoalveolar lavage fluid showed a severe, persistent inflammatory response in the DQ 12 group. Significant, but lower effects were observed in the zeolite mid and high dose groups, i.e. for total protein in males. This effect disappeared in the recovery period. Neutrophil levels in BAL were moderately or highly increased in the zeolite low, mid and high dose groups. These values did not recover in the post-observation period. However, in terms of absolute cell numbers, the PMN number was 15-fold higher in the DQ 12 than in the zeolite high dose group.
- Among organs lung wet weights of the DQ 12 group were the only tissue showing significantly increased values as compared to controls.
- Histopathology showed statistically significant exposure-related findings only in lungs and lung-associated lymph nodes (LALN). Pulmonary inflammation was most pronounced in

the quartz DQ 12 group, followed by the 10 mg/m³, 1.9 mg/m³ and 0.45 mg/m³ zeolite groups and the TiO₂ group. In the quartz DQ 12 group inflammation was also qualitatively different as compared to the zeolite groups, i.e. findings such as alveolar lipoproteinosis, formation of cholesterol granulomas and the 'mixed type' of bronchiolo-alveolar hyperplasia were unique for this group.

Recovery effects of interstitial mononuclear cell infiltration and alveolar/interstitial macrophage accumulation occurred after 3 months only in the zeolite and TiO₂ groups, but not in the quartz group. With respect to alveolar granulocytic infiltration, bronchiolo-alveolar hyperplasia and interstitial fibrosis, no differences were observed in the zeolite and TiO₂ groups. In contrast, the quartz DQ 12 group showed a tendency towards increased collagen deposition after 3 months of recovery.

- The proliferation assay of lung parenchyma resulted in a significant dose-dependent increase of indices in the female zeolite groups (males: not significant). Upon 3 months recovery significance was observed in the female high dose group only. The DQ 12 groups showed a response higher by a factor of 2 to 3 as compared to the zeolite high groups.
- Biological effects of the test substances can be ranked in the following order:
Quartz DQ 12 >> Zeolite high > Zeolite mid > TiO₂ > Zeolite low > Control
- The No Observed Adverse Effect Level (NOAEL) of the tested zeolite analog was ≤ 0.45 mg/m³ after a 3-month nose-only inhalation in rats.

The effects are collected and graded in Table 1.

Table 1 Summary of main effects after a subchronic inhalation period

Test substance	Effects after end of exposure (0 month) and after end of the recovery period (3 months)									
	Zeolite low		Zeolite mid		Zeolite high		Quartz DQ 12		TiO ₂	
Post-Treatment Period (months)	0	3	0	3	0	3	0	3	0	3
Parameter										
Increase of lung weight	-	-	-	-	-	-	+++	+++	-	-
Retardation of lung clearance	-	-	-	-	- /	- /	+++	+++	- /	- /
Pulmonary inflammation (BAL)	+	/	++	++	+++	+++	+++	+++	-	-
Interstitial/peribronchiolar fibrosis	-	-	-	/	+	+	++	+++	-	-
Proliferation of alveolar parenchymal cells	-	-	/	-	/	/	+++	+++	-	-
Proliferation of terminal bronchiolar epithelium	-	-	-	-	-	-	+++	++	-	-

+ very slight or slight effect
 ++ moderate effect
 +++ high effect
 - not significant
 / equivocal

ABSTRACT

Male and female Wistar WU rats, a total of 372 animals were exposed nose-only 6 hours/day, 5 days/week for 3 months (65 total days of exposure) to zeolite aerosol concentrations of 0.45, 1.9 and 10 mg/m³. Concurrent clean air, positive and negative control groups inhaled filtered air, 7.2 mg/m³ quartz DQ 12 and 6.3 mg/m³ titanium dioxide, respectively, to compare and rank the effects to these well-characterized substances. Since different mass median aerodynamic diameters (MMAD) were determined prior to exposure start for the zeolite low, mid, high, quartz DQ12 and titanium dioxide groups, the aerosol concentrations were adjusted with the zeolite high group as basis (10 mg/m³) to achieve the desired same retained lung burdens in the high dose groups. Upon cessation of exposure, a 3-month post-treatment observation followed.

Animals tolerated the exposure conditions well, i.e. the animal clinical status was within normal limits. From the total number of 372 rats within the study 9 unscheduled deaths among all groups were observed which are considered to be incidental findings in this strain.

Body weight and food consumption measurements did not show significant changes.

Analysis of lung retention of test substances in lungs resulted in data elucidating that the objective of the study to have mostly the same lung burdens in the three high dose groups was achieved. In males about 1100 µg/rat and in females about 1000 µg/rat of test substances were retained. These lung burdens are in the range that the lung clearance capacity is slightly retarded. Overall, by evaluating the retention data after 3 months of recovery, an actual lung clearance retardation was barely seen, with the exception of the DQ 12 group where clearance totally collapsed.

Bronchoalveolar lavagate (BAL) analysis revealed levels of polymorphonuclear neutrophils of 12%, 40% and 49% (sexes pooled) in the zeolite low, mid and high dose group 1 day after termination of exposure. In the DQ12 and titanium dioxide group the values were 51% and 0.5%. After three months recovery the corresponding data were 10%, 35% and 56% in the zeolite groups and 58% and 1.6% in the quartz and TiO₂ groups. These data demonstrate that the zeolite low exposure group showed slightly increased values even after the recovery period. The zeolite mid and high concentration induced a moderate to severe lung inflammation in lungs persisting for 3 months. However, the response was significantly

weaker than that of the DQ 12 group (zeolite mid and high after 1 day/zeolite mid after 3 months). Thus, there seems to exist a substantial difference of the inflammatory potential between DQ 12 and the zeolite groups. This conclusion is confirmed by the 15 times higher absolute leukocyte numbers in the DQ 12 groups.

Histopathological examination showed statistically significant exposure-related findings only in the lungs and LALN. There was no evidence of a systemic effect of the test substances used. Pulmonary inflammation was most pronounced in the quartz DQ 12 group, followed by the 10 mg/m³, 1.9 mg/m³ and 0.45 mg/m³ zeolite groups and the TiO₂ group. It has to be emphasized, however, that pulmonary inflammation in the quartz group was not only much more prominent but also qualitatively different as compared to the type of inflammation seen in the zeolite groups. Findings such as alveolar lipoproteinosis, formation of cholesterol granulomas and the 'mixed type' of bronchiolo-alveolar hyperplasia were unique for the quartz group. The degree of inflammation in the low dose (0.45 mg/ m³) zeolite group and the TiO₂ group was very low and almost similar as reflected by the absence of interstitial fibrosis in both groups.

A comparison of the 2 postexposure groups revealed that only interstitial mononuclear cell infiltration and alveolar/interstitial macrophage accumulation seemed to have slightly decreased from the 1-day towards the 3-month timepoint, but only in the zeolite and TiO₂ groups and not in the quartz group. With respect to alveolar granulocytic infiltration, bronchiolo-alveolar hyperplasia and interstitial fibrosis, there were no obvious differences (i.e. neither a recovery effect nor strengthening of effects) between the 2 zeolite and TiO₂ postexposure groups. In contrast, the results show a tendency towards increased collagen deposition in the quartz group at the 3-month postexposure timepoint.

The 6-bromo-deoxyuridine (BrdU) proliferation assay on lung parenchyma resulted in both sexes in a dose-dependent increase of indices in the zeolite groups (about 2.8, 4.5 and 6.5% vs. about 2.5% in controls 8 days after termination of exposure; all pooled data). In the female mid and high dose groups this increase was statistically significant. In the DQ 12 group the value was about 14%. Upon 3 months of recovery the indices lowered and only the female zeolite high group remained significantly increased compared to controls. The DQ 12 groups differed significantly from the zeolite mid and high dose groups at all time-points. In terminal bronchiolar epithelium the zeolite groups did not show clear significant increases.

Again, the DQ 12 groups were significantly increased compared to controls (with the exception of day 91, females).

In summary, DQ 12 groups showed responses stronger by a factor of 2 to 3 as compared to the zeolite high groups demonstrating a substantial difference in the proliferative potency of these test substances.

Biological effects of the test substances can be ranked in the following order:

Quartz DQ 12 >> Zeolite high > Zeolite mid > TiO₂ > Zeolite low > Control

The **No Observed Adverse Effect Level (NOAEL)** was $\leq 0.45 \text{ mg/m}^3$ zeolite after a 3-month nose-only exposure in rats.