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**RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT**

**FINAL REPORT**

**IITRI Project No. L08100  
Study No. 1277B**

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RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT

Study No. 1277B

This report summarizes inhalation research projects conducted by IIT Research Institute (IITRI) for the Amoco Corporation.

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RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT

Study No. 1277B

SUMMARY

The study consisted of two parts. The first part included two groups of 10 male and 10 female Sprague-Dawley rats each; one of which was exposed to Phthalic Anhydride (PA) as a particulate aerosol at a target concentration of  $500 \mu\text{g}/\text{m}^3$  PA, 6 hours/day for 5 days. The other group was a nonexposed control. Following a 3-week rest period, the PA-exposed group was challenged with the same concentration of PA for 6 hours. The second group was not challenged. In the second part of the study, two groups of 12 male rats each were exposed to  $500 \mu\text{g}/\text{m}^3$  PA, 6 hours/day for 5 days. Following a 3-week rest period, one of the groups was challenged with a single inhalation exposure to  $500 \mu\text{g}/\text{m}^3$  of Trimellitic Anhydride (TMA). The other group was not challenged.

The analytical time-weighted average concentrations of PA for the five part 1 and part 2 exposures and one challenge were 525 and  $481 \mu\text{g}/\text{m}^3$ , respectively. The time-weighted average challenge concentration of TMA was  $317 \mu\text{g}/\text{m}^3$ .

None of the rats died during the study. In the PA-exposed/PA-challenged rats, 7/10 males and 3/10 females responded with increased numbers (*i.e.*,  $\geq 10/\text{lung}$ ) of external hemorrhagic lung foci compared to 0/20 animals in the control group. Statistically significant increases in number of foci/lung and PA-specific serum IgG antibody were observed in PA-exposed and challenged rats compared to nonchallenged controls. Females had significantly higher serum IgG antibody levels, but significantly lower numbers of lung foci than did males after PA-challenge. Minimal to mild parabronchial lymphoid hyperplasia, alveolar hemorrhage and perivascular acute and chronic inflammation were present in one or two of the three PA-challenged rats examined. Microscopic lung lesions were absent from the control group. Thus, significant increases in lung lesions and PA-specific IgG antibody levels indicated that PA induces respiratory sensitization in the rat.

PA-exposed/TMA-challenged males had significantly increased numbers of foci/lung, as well as more animals per group (5/12) with more than 10 lung foci (*i.e.*, positive response), compared to the PA-exposed/nonchallenged males (1/12). Both groups had serum IgG antibody levels comparable to those of the PA-exposed/challenged males of part 1, and they were all significantly increased compared to the part 1 male controls. The TMA-challenged males had significantly fewer foci/lung than the PA-challenged males. Microscopic lung lesions were similar (*i.e.*, minimal to mild alveolar hemorrhage and perivascular acute and chronic inflammation in one or two rats) in the TMA-challenged rats compared to the PA-challenged rats. PA-exposed/nonchallenged rats had no microscopic lung lesions. Thus, there exists a cross-sensitization reaction between PA and TMA, and except for fewer external hemorrhagic lung foci, the response elicited by TMA-challenge was similar to that in PA-challenged rats with regard to the incidence and severity of lung lesions and the levels of serum IgG antibody.

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RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT

I. TEST ARTICLE

Phthalic Anhydride (PA) was purchased from Aldrich Chemical Co. (Lot No. 00103DL). It was a white powder and was ground to respirable-sized particles using a mortar and pestle.

II. GENERAL METHODS

A. Test Article Generation: Respirable-sized PA particles were aerosolized in a modified TSI Fluidized Bed Aerosol Generator (Model 3400, TSI, Inc., St. Paul, MN) and blown by means of a Transvector Jet (Model 901B, Vortex Corp., Cincinnati, OH) into the inhalation chamber.

The PA aerosol entered the exposure chamber through the top via a venturi tube and exited through a pipe located near the bottom of the chamber. The chamber air was exhausted through a filtering system before being discharged to the outside environment.

B. Test Atmosphere Monitoring: Particles from measured volumes of test atmospheres were trapped onto filter pads, extracted into 10% (v/v) acetonitrile in water, and analyzed using a UV/VIS Spectrophotometer (Perkin-Elmer Model Lambda 5) set at a wavelength of 228 nm. The resultant absorbances were compared to those of known standards for quantitation. Challenge concentrations of TMA were determined similarly except at a wavelength of 238 nm.

C. Daily Observations: The rats were observed daily during the study for mortality and morbidity.

D. Body Weights: Body weights were measured prior to study initiation and weekly thereafter to monitor the rats' general well-being. However, because the controls were not fasted in the cage, they could not be compared to the PA-exposed and challenged rats.

E. Postmortem Examination Procedures: Approximately 18 hours following the challenge exposure, the rats were anesthetized with sodium pentobarbital and blood samples were obtained from the femoral artery of each animal just prior to scheduled sacrifice. A gross necropsy was performed on all rats. The lungs were removed, trimmed of excess adherent tissue, weighed and examined for external hemorrhagic foci. The lung volume was determined by liquid displacement and the lungs were inflated with and saved in 10% neutral buffered formalin. The lungs from designated rats (3/group) were examined microscopically by the study pathologist.

- F. Serum Antibody Determinations: The serum from each rat was analyzed using an Enzyme-Linked Immunosorbent Assay (ELISA). ELISA determinations were performed using polystyrene microtiter plates (Geiner Microtiter Plates, Nurtigen, Germany). The plates were coated with 200  $\mu$ l aliquots of antigen, PA-rat serum albumin (RSA), and RSA diluted to 150  $\mu$ g/ml in carbonate buffer (pH 9.6) for 1 hour at 37°C. The plates were washed between steps with Tween in phosphate buffered saline (PBS). Class-specific antibody studies were performed utilizing a double antibody technique. Serum samples from exposed animals and controls were adjusted by dilution with PBS-Tween to 0.5, 0.05, and 0.005 mg/l albumin. A 200  $\mu$ l aliquot was pipetted onto each well which was coated with PA-RSA and incubated at 37°C for 1 hour. The IgG assay was performed using a rabbit anti-rat IgG (Cooper Biochemical, Malvern, PA) as the first antibody and goat anti-rabbit gamma globulin conjugated with alkaline phosphatase (Sigma Chemical, St. Louis, MO) as the second antibody. Each layer was allowed to incubate at 37°C for 1 hour. Dinitrophenyl phosphate (Sigma Chemical; 1 mg/ml in diethanolamine buffer) was added and the colorimetric response was measured as the optical density at 405 nm using an Artek Model 210 optical scanner (Artek Systems, Farmingdale, NY).

### III. EXPERIMENTAL DESIGN

- A. Part 1: The purpose of this experiment was to determine the respiratory sensitization potential of PA in rats.

Two groups of 10 male and 10 female Sprague-Dawley rats (Charles River Laboratories, Portage, MI) each were utilized in this part of the study. One group was exposed to a target concentration of 500  $\mu$ g/m<sup>3</sup> of PA, 6 hours/day for 5 days. The second group was not exposed and served as an unchallenged control. The PA-exposed rats were rested for 3 weeks and then challenged with PA at the same target concentration for 6 hours. The treated rats as well as the untreated control rats were euthanized and subjected to a limited necropsy approximately 18 hours following the challenge exposure.

The lungs from two male rats and one female rat from each of the treated and control groups were processed and examined microscopically.

- B. Part 2: The purpose of this experiment was to determine if cross-sensitization between PA and Trimellitic Anhydride (TMA) can occur.

Two groups of twelve male Sprague-Dawley rats (Charles River Laboratories, Portage, MI) were utilized in this part of the study. Both groups were exposed to PA at a target concentration of 500  $\mu$ g/m<sup>3</sup>, 6 hours/day for 5 days. The rats were rested 3 weeks and one group was challenged with TMA at 500  $\mu$ g/m<sup>3</sup> for 6 hours, while

the other group was not challenged. All rats were euthanized and subjected to a limited necropsy approximately 18 hours following the challenge exposure.

The lungs from three TMA-challenged and three nonchallenged male rats were processed and examined microscopically.

#### IV. RESULTS

- A. Part 1: The time-weighted average concentration of PA was  $525 \mu\text{g}/\text{m}^3$  (range of  $404$  to  $746 \mu\text{g}/\text{m}^3$ ) for the five exposure days, and  $481 \mu\text{g}/\text{m}^3$  for the challenge exposure.

Means of 20 and 11 external hemorrhagic foci/lung were counted in the male and female PA-exposed rats, respectively, which were significantly increased over those in the controls (Table 1). Seven males and 3 females in the PA-exposed group were considered to have responded positively (*i.e.*, having  $\geq 10$  foci/lung), while no positive responses were observed in the control group. Additionally, there were statistically significant increases in PA-specific serum IgG antibody levels in the PA-exposed male and female rats, with females having higher antibody levels than males.

Microscopic examination of the lungs from select PA-treated rats revealed minimal to mild parabronchial lymphoid hyperplasia, alveolar hemorrhage and perivascular acute and chronic inflammation in 1/3, 2/3, and 1/3 of the rats, respectively. No microscopic lesions were observed in the lungs from the three select control rats.

- B. Part 2: The rats were exposed to the same PA aerosol concentrations in air as above (*i.e.*, time-weighted average concentration =  $525 \mu\text{g}/\text{m}^3$ ; range =  $404$  to  $746 \mu\text{g}/\text{m}^3$ ) for the five exposure days. Rats were challenged with TMA at a time-weighted average concentration of  $317 \mu\text{g}/\text{m}^3$ .

Means of 4 and 10 foci/lung were seen in the PA-exposed/nonchallenged rats and PA-exposed/TMA-challenged rats, respectively (Table 1). Five (5/12) PA-exposed/TMA-challenged rats were considered to have positively responded (*i.e.*, having  $\geq 10$  foci/lung) compared to only one PA-exposed/nonchallenged rat. The number of foci/lung in the PA-exposed/TMA-challenged group was significantly increased compared to the nonchallenged control males of part 1, but was significantly decreased compared to that of the PA-challenged group of part 1.

Serum IgG antibody levels were similar in the two groups and the serum IgG levels of both were significantly increased over those of the nonchallenged control males. There was no significant difference between the PA-challenged, the TMA-challenged and the nonchallenged PA-exposed rats with regard to serum IgG antibody levels.

Microscopic examination of the lungs from select PA-exposed/TMA-challenged rats revealed minimal to mild alveolar hemorrhage and perivascular acute and chronic inflammation. No microscopic lesions were present in the lungs from the select PA-exposed/nonchallenged rats.

V. CONCLUSIONS

Rats exposed to a target concentration of 500  $\mu\text{g}/\text{m}^3$  of PA for 5 days (6 hours/day), rested for 3 weeks, and challenged with PA exhibited significant increases in lung lesions and PA-specific IgG antibody. Rats challenged with TMA following a 5-day exposure to PA and a 3-week rest period exhibited similar increases in the incidence and severity of lung lesions and levels of serum IgG antibody. These findings indicate that Phthalic Anhydride induces respiratory sensitization in rats and that it cross reacts with TMA.

**TABLE**

**RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT**

TABLE 1

Summary of Lung Parameters and Serum IgG Antibody

Exposure/ Challenge	Body Weight (g)	Absolute Lung Weight (g)	PART 1		Lung Foci	Serum IgG Antibody O.D. <sup>c</sup> 1:900 Dil.	
			Relative Lung Weight <sup>a</sup>	Absolute Lung Volume (ml)			
<b>MALES</b>							
PA/PA	366 ± 22.9 <sup>d</sup>	1.39 ± 0.11	0.38 ± 0.02	1.9 ± 0.1	20 ± 14.4*	0.596 ± 0.307*	
Control/None	379 ± 22.9	1.41 ± 0.10	0.37 ± 0.02	1.9 ± 0.1	4 ± 2.2	0.004 ± 0.005	
<b>FEMALES</b>							
PA/PA	269 ± 11.5	1.29 ± 0.11	0.48 ± 0.04	1.8 ± 0.2	11 ± 14.4*	0.801 ± 0.205*	
Control/None	271 ± 18.6	1.22 ± 0.11	0.45 ± 0.03	1.7 ± 0.2	2 ± 1.8	0.023 ± 0.021	
PART 2							
Exposure/ Challenge	Body Weight (g)	Absolute Lung Weight (g)	Relative Lung Weight	Absolute Lung Volume (ml)	Relative Lung Volume	Lung Foci	Serum IgG Antibody O.D. 1:900 Dil.
PA/TMA	377 ± 20.9	1.39 ± 0.08	0.37 ± 0.02	1.9 ± 0.1	0.51 ± 0.04	10 ± 8.2*	0.595 ± 0.228*
PA/None	381 ± 20.0	1.39 ± 0.12	0.37 ± 0.03	1.9 ± 0.1	0.51 ± 0.03	4 ± 3.1	0.458 ± 0.340*

<sup>a</sup> Relative lung weight = [lung weight (g)/body weight (g)] x 100

<sup>b</sup> Relative lung volume = [lung volume (ml)/body weight (g)] x 100

<sup>c</sup> O.D. = Optical Density

<sup>d</sup> Values represent mean ± standard deviation

\* Significantly different from controls, p ≤ 0.05

**APPENDICES**

**RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT**

**APPENDIX 1**

**Individual Male Lung Parameters and Serum Antibody  
Part 1  
PA-Treated Group**

<u>Animal Number</u>	<u>Body Weight (g)</u>	<u>Lung Weight (g)</u>	<u>Relative Lung Weight<sup>a</sup></u>	<u>Lung Volume (ml)</u>	<u>Relative Lung Volume<sup>b</sup></u>	<u>Lung Foci</u>	<u>IgG Antibody O.D.<sup>c</sup> 1:900 Dil.</u>
301	358	1.36	0.38	1.8	0.50	34	0.261
302	368	1.33	0.36	1.7	0.46	17	0.456
303	403	1.48	0.37	2.1	0.52	17	0.260
304	386	1.57	0.41	2.0	0.52	26	1.038
305	331	1.22	0.37	1.8	0.54	5	0.174
306	333	1.27	0.38	1.9	0.57	53	0.921
307	360	1.40	0.39	2.0	0.56	8	0.796
308	382	1.37	0.36	2.0	0.52	16	0.857
309	380	1.52	0.40	2.1	0.55	16	0.504
310	357	1.33	0.37	1.9	0.53	9	0.689

<sup>a</sup> Relative lung weight = [lung weight (g)/body weight (g)] x 100

<sup>b</sup> Relative lung volume = [lung volume (ml)/body weight (g)] x 100

<sup>c</sup> O.D. = Optical Density

**RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT**

APPENDIX I (cont.)

Individual Male Lung Parameters and Serum Antibody  
Part I  
Control/Nonchallenged Group

Animal Number	Body Weight (g)	Lung Weight (g)	Relative Lung Weight <sup>a</sup>	Lung Volume (ml)	Relative Lung Volume <sup>b</sup>	Lung Foci	IgG Antibody O.D. <sup>c</sup> 1:900 Dil.
321	373	1.62	0.43	2.1	0.56	4	0.002
322	359	1.33	0.37	1.7	0.47	6	0.001
323	351	1.26	0.36	1.8	0.51	2	0.002
324	403	1.43	0.35	1.9	0.47	3	0.001
325	377	1.39	0.37	1.8	0.48	2	0.001
326	377	1.41	0.37	1.8	0.48	2	0.001
327	371	1.36	0.37	1.8	0.49	3	0.018
328	377	1.38	0.37	1.8	0.48	2	0.003
329	432	1.48	0.34	2.0	0.46	6	0.008
330	374	1.39	0.37	2.0	0.53	8	0.005

<sup>a</sup> Relative lung weight = [lung weight (g)/body weight (g)] x 100

<sup>b</sup> Relative lung volume = [lung volume (ml)/body weight (g)] x 100

<sup>c</sup> O.D. = Optical Density

**RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT**

**APPENDIX 2**

**Individual Female Lung Parameters and Serum Antibody  
Part I  
PA-Treated Group**

<u>Animal Number</u>	<u>Body Weight (g)</u>	<u>Lung Weight (g)</u>	<u>Relative Lung Weight<sup>a</sup></u>	<u>Lung Volume (ml)</u>	<u>Relative Lung Volume<sup>b</sup></u>	<u>Lung Foci</u>	<u>IgG Antibody O.D.<sup>c</sup> 1:900 Dil.</u>
311	253	1.26	0.50	1.9	0.75	0	0.889
312	257	1.16	0.45	1.7	0.66	3	1.095
313	265	1.36	0.51	2.2	0.83	6	0.695
314	264	1.12	0.42	1.6	0.61	1	0.851
315	276	1.16	0.42	1.6	0.58	5	0.499
316	281	1.41	0.50	1.9	0.68	16	0.636
317	292	1.45	0.50	2.0	0.68	22	0.546
318	264	1.35	0.51	1.8	0.68	46	1.024
319	272	1.32	0.49	1.8	0.66	6	0.787
320	270	1.33	0.49	1.8	0.67	0	0.992

- <sup>a</sup> Relative lung weight = [lung weight (g)/body weight (g)] x 100
- <sup>b</sup> Relative lung volume = [lung volume (ml)/body weight (g)] x 100
- <sup>c</sup> O.D. = Optical Density

**RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT**

APPENDIX 2 (cont.)

Individual Female Lung Parameters and Serum Antibody  
Part I  
Control/Nonchallenged Group

<u>Animal Number</u>	<u>Body Weight (g)</u>	<u>Lung Weight (g)</u>	<u>Relative Lung Weight<sup>a</sup></u>	<u>Lung Volume (ml)</u>	<u>Relative Lung Volume<sup>b</sup></u>	<u>Lung Foci</u>	<u>IgG Antibody O.D.<sup>c</sup> 1:900 Dil.</u>
331	272	1.20	0.44	1.6	0.59	1	0.013
332	254	1.14	0.45	1.7	0.67	0	0.020
333	282	1.14	0.40	1.7	0.60	1	0.024
334	316	1.48	0.47	2.0	0.63	6	0.004
335	274	1.25	0.46	1.8	0.66	2	0.000
336	270	1.28	0.47	1.9	0.70	0	0.027
337	255	1.18	0.46	1.8	0.71	1	0.031
338	253	1.25	0.49	1.8	0.71	0	0.076
339	271	1.20	0.44	1.6	0.59	2	0.020
330	261	1.10	0.42	1.4	0.54	2	0.013

<sup>a</sup> Relative lung weight = [lung weight (g)/body weight (g)] x 100

<sup>b</sup> Relative lung volume = [lung volume (ml)/body weight (g)] x 100

<sup>c</sup> O.D. = Optical Density

**RESPIRATORY SENSITIZATION STUDY OF  
PHTHALIC ANHYDRIDE (PA): A RESEARCH PROJECT**

**APPENDIX 3**

**Individual Lung Parameters and Serum Antibody  
Part 2**

Animal Number	Body Weight (g)	Lung Weight (g)	Relative Lung Weight <sup>a</sup>	Lung Volume (ml)	Relative Lung Volume <sup>b</sup>	Lung Foci	IgG Antibody O.D. <sup>c</sup> 1:900 Dil.
<b>PA-Exposed/Nonchallenged Group</b>							
353	353	1.26	0.36	1.8	0.51	0	0.401
354	364	1.39	0.38	1.8	0.49	8	0.479
355	406	1.45	0.36	1.9	0.47	2	0.868
356	413	1.56	0.38	2.1	0.51	11	0.998
357	394	1.60	0.41	2.2	0.56	5	0.117
358	361	1.33	0.37	1.8	0.50	2	0.362
359	380	1.36	0.36	1.8	0.47	2	0.064
360	399	1.38	0.35	2.1	0.53	3	0.069
361	368	1.47	0.40	1.9	0.52	1	0.463
362	359	1.23	0.34	1.9	0.53	2	0.916
363	382	1.23	0.32	1.9	0.50	4	0.660
364	393	1.46	0.37	1.9	0.48	5	0.099
<b>PA-Exposed/TMA-Challenged Group</b>							
341	382	1.34	0.35	1.7	0.45	9	0.427
342	351	1.36	0.39	1.9	0.54	6	0.505
343	371	1.46	0.39	2.0	0.54	21	0.846
344	415	1.51	0.36	2.1	0.51	30	0.921
345	359	1.41	0.39	2.0	0.56	10	0.398
346	402	1.52	0.38	2.0	0.50	11	0.512
347	352	1.32	0.38	1.9	0.54	1	0.685
348	390	1.37	0.35	2.1	0.54	10	0.603
349	380	1.34	0.35	2.0	0.53	5	0.275
350	391	1.42	0.36	1.9	0.49	6	0.325
351	384	1.26	0.33	1.7	0.44	3	0.956
352	352	1.28	0.36	1.8	0.51	5	0.682

<sup>a</sup> Relative lung weight = [lung weight (g)/body weight (g)] x 100

<sup>b</sup> Relative lung volume = [lung volume (ml)/body weight (g)] x 100

<sup>c</sup> O.D. = Optical Density

APPENDIX 4

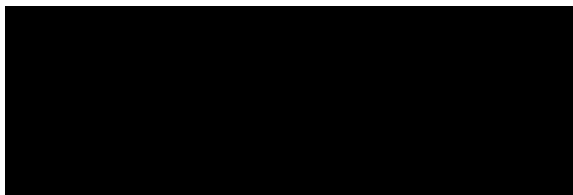
Study Number 1277B

PATHOLOGY SUMMARY

Lungs from 3 animals from the following treatment groups were examined microscopically:

<u>Exposure/Challenge</u>	<u>No. of Animals Examined (Sex)</u>
Control/None	3 (2 M, 1 F)
PA/None	3 (3 M)
PA/PA	3 (2 M, 1 F)
PA/TMA	3 (3 M)

No microscopic lesions were observed in any of the Control/nonchallenged or PA-exposed/nonchallenged rats. Alveolar hemorrhage, parabronchial lymphoid hyperplasia, and perivascular acute and chronic inflammation were observed in 2/3, 1/3 and 1/3 PA-exposed/PA-challenged animals, respectively. Alveolar hemorrhage and perivascular acute and chronic inflammation were also seen in 1/3 and 2/3 PA-exposed/TMA-challenged rats, respectively. These lesions were all considered evidence of a pulmonary sensitization reaction, although the lesions were of minimal or mild severity in all animals. Thus, lung lesions consistent with a sensitization reaction were present in one or two animals sensitized to phthalic anhydride and then challenged with either phthalic anhydride or trimellitic anhydride; however, the response observed for both PA and TMA challenge was slight.



radiologist

4-3-91  
Date

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