

CHAPTER 20

PULMONARY DISEASE

INTRODUCTION

Pulmonary dysfunction and overt pulmonary disease are not recognized clinical entities resulting from exposure to chlorophenols or TCDD.

Acute exposure to chlorophenols, phenoxy herbicides, and TCDD, have caused the traditional acute symptoms of cough, nasal/lung irritation, shortness of breath, and, occasionally, bronchitis. These symptoms have been noted almost exclusively in industrial workers and not in individuals experiencing casual contact. Long-term sequelae arising from the acute symptom stage in ill individuals have not been generally known because of minimal followup and surveillance of the pulmonary symptoms.

Only one contemporary morbidity study has attributed pulmonary dysfunction to phenoxy herbicide and TCDD exposure.¹ The percent abnormal pulmonary parameters of forced expiratory volume (FEV), forced vital capacity (FVC), forced expiratory volume in one second (FEV₁)/FVC ratio, and forced midexpiratory flow rate (FEF₂₅₋₇₅) were significantly higher in exposed workers who currently smoke, than in nonexposed workers who smoke. In considerable contrast, these test parameters were essentially equal in nonsmokers and former smokers of both the exposed and nonexposed groups. The effect of current smoking persisted after a logistic regression analysis adjusting for pack-years of cigarette smoking. Adjusted means of the test parameters FEV, FVC, and FEV₁/FVC also showed significant differences for current smokers but not for nonsmokers or former smokers.

As with other nonclassical clinical endpoints, prior investigators perhaps undervalued the incorporation of pulmonary disease and function into their study protocols.

Further, due to the profound effect of smoking on pulmonary function, great emphasis must be placed in the collection of highly accurate, detailed, and validated smoking data as an adjustment variable, a process that is not straightforward in today's environment of antismoking.

The only recent data comparable to this study are found in the 1984 AFHS Baseline Morbidity Report, which is reviewed below.²

Baseline Summary Results

The 1982 Baseline examination explored historical pulmonary disease by questionnaire and active pulmonary function by standardized spirometric technique at the physical examination. These areas were of significant interest because of routine operational inhalation of Herbicide Orange by all Ranch Hand flying crewmen as well as ground maintenance personnel (Baseline Report Chapter 1, Buckingham).

The questionnaire revealed no group differences for historical diagnoses of tuberculosis and fungal infections, pneumonia, cancer, or chronic sinusitis and upper respiratory disease. At the physical examination the unadjusted means for FEV₁ (percent predicted), FVC, and the FEV₁/FVC ratio were almost identical between the Ranch Hands and Comparisons. Adjusted mean values were not calculated due to significant interactions (age, group, and pulmonary function for FEV₁ and FVC; smoking with FEV₁/FVC).

Detailed exposure analyses showed two significant associations in the enlisted flyer and enlisted groundcrew strata, but neither was indicative of linear dose response. Attempts to adjust the means of the pulmonary function values for age and smoking revealed several interactions, but essentially negative results.

Overall, there were no pulmonary disease or pulmonary function data or associations of concern.

Parameters of the 1985 Pulmonary Examination

Because of the essentially negative pulmonary analyses from the Baseline examination, pulmonary function (spirometric) studies were not performed during the first followup examination. Collection of pulmonary data was limited to a questionnaire history of respiratory disease, physical examination of the thorax and lungs, and pulmonary abnormalities detected on a routine chest x ray.

Thus, the data analyses consist of group assessments of respiratory disease incidence, physical examination abnormalities, and the current prevalence of x-ray abnormalities. Covariate adjustments are made for age and smoking (yes, no, former, and pack-years). Minor numeric differences in the tables are due to rare missing dependent variable or covariable data. The analyses are based on 1,016 Ranch Hands and 1,293 Comparisons. No exclusions based on clinical conditions were made.

Mortality due to respiratory disease, as of 31 December 1985, in the Ranch Hand and the 1:5 matched Comparison cohort is summarized. Morbidity data are analyzed using linear and loglinear models.

RESULTS AND DISCUSSION

Mortality Experience

The mortality of the Ranch Hand and Comparison groups through 31 December 1985 was evaluated. There were seven deaths from respiratory system conditions in the Comparison group and none in the Ranch Hand group. This analysis was based on the 1:5 Ranch Hand to Comparison mortality study cohorts. Two of these deaths were Comparison flying officers, three were enlisted flyers, and the remaining two were enlisted groundcrew.

Unadjusted Morbidity Analyses

Analyses were performed on the history of respiratory illnesses as provided by the participants during the physical examination. The results of the

radiological and clinical examination of the lungs and chest were also analyzed. These unadjusted analyses are summarized in Tables 20-1 and 20-2.

As shown, no significant group differences were observed for history of asthma, bronchitis, pleurisy, pneumonia, or tuberculosis. Similar non-significant results were found in the evaluation of the clinical variables.

Parallel analyses were conducted using data from the Original Comparisons, with comparable results (Appendix R, Table R-1).

Adjusted Morbidity Analyses

Statistical adjustment for the effects of age and lifetime smoking did not alter the findings of group similarity seen in the unadjusted analyses. Lifetime smoking was categorized as nonsmoking (0 pack-years), moderate (greater than 0 to 10 pack-years) and heavy (greater than 10 pack-years). These results are shown in Table 20-3.

Lifetime smoking consistently exerts significant effects on nearly all historical illness and clinical examination variables, and age was an important factor for the history of pneumonia and the clinical assessment of thorax and lungs (representing an overall clinical assessment of normality/abnormality in the respiratory system), chest asymmetry, the presence of hyperresonance, rales, and the presence of x-ray abnormality.

There were significant or borderline significant group-by-pack-year interactions in analyses of a history of pleurisy and tuberculosis, for the presence of rales on examination, and for x-ray abnormality. There was also an interaction for asthma of borderline significance ($p=0.068$). A significant group-by-age interaction was seen for the presence of rales. The results of analyses stratified to clarify these interactions are shown in Table 20-4.

Nonsmoking Ranch Hands had significantly more asthma ($p=0.050$) than their nonsmoking Comparisons, while the history of asthma was not significantly different in either category of smokers. Pleurisy was significantly more frequent in moderately smoking Ranch Hands ($p=0.0001$), but bordered on being significantly increased in heavily smoking Comparisons ($p=0.060$). Analyses of a history of tuberculosis and the presence of rales was hampered by small numbers of cases in both groups (a total of 13 cases). The presence of several cells containing zeros makes interpretation of these analyses extremely difficult. Except in those strata with zero cells, no statistical significance was noted. In the analysis of x-ray abnormalities, the nonsmoking Ranch Hands had significantly less abnormality ($p=0.030$) than the nonsmoking Comparisons. Analyses of other strata did not reveal any significant group differences.

These adjusted analyses were performed on data from the Original Comparisons, with similar results (see Tables 20-2 and 20-3).

EXPOSURE ANALYSES

The pulmonary data from the Ranch Hands were analyzed using the exposure index as a covariate (categorized as high, medium, or low within each occupational stratum). The percent abnormality at each level of exposure for each clinical or historical variable is presented in Tables 20-5, 20-6, and 20-7.

TABLE 20-1.

Unadjusted Analyses of Reported History of Respiratory Illness by Group

Variable	Statistic	Group				Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand		Comparison			
		Number	Percent	Number	Percent		
Asthma	n	1,016		1,292		1.12 (0.74,1.70)	0.58
	Abnormal	44	4.3	50	3.9		
	Normal	972	95.7	1,242	96.1		
Bronchitis	n	1,015		1,292		0.97 (0.76,1.25)	0.84
	Abnormal	129	12.7	168	13.0		
	Normal	886	87.3	1,124	87.0		
Pleurisy	n	1,016		1,291		1.05 (0.71,1.56)	0.81
	Abnormal	47	4.6	57	4.4		
	Normal	969	95.4	1,234	95.6		
Pneumonia	n	1,016		1,291		1.01 (0.82,1.25)	0.89
	Abnormal	195	19.2	245	19.0		
	Normal	821	80.8	1,046	81.0		
Tuberculosis	n	1,015		1,292		1.49 (0.52,4.28)	0.48
	Abnormal	7	0.7	6	0.5		
	Normal	1,008	99.3	1,286	99.5		

TABLE 20-2.

Unadjusted Analyses of Radiological and Clinical Respiratory System Findings by Group

Variable	Statistic	Group		Est. Relative Risk (95% C.I.)	p-Value		
		Ranch Hand	Comparison				
		Number	Percent	Number	Percent		
Thorax and Lungs	n	1,015		1,293			
	Abnormal	61	6.0	61	4.7	1.29 (0.90,1.86)	0.17
	Normal	954	94.0	1,232	95.3		
Asymmetrical Expiration	n	1,015		1,293			
	Abnormal	2	0.2	3	0.2	0.85 (0.17,4.45)	0.86
	Normal	1,013	99.8	1,290	99.8		
Hyperresonance	n	1,015		1,293			
	Abnormal	30	3.0	35	2.7	1.09 (0.67,1.79)	0.72
	Normal	985	97.0	1,258	97.3		
Dullness	n	1,015		1,293			
	Abnormal	2	0.2	1	0.1	2.55 (0.31,17.62)	0.43
	Normal	1,013	99.8	1,292	99.9		
Wheezes	n	1,015		1,293			
	Abnormal	24	2.4	21	1.6	1.47 (0.82,2.63)	0.20
	Normal	991	97.6	1,272	98.4		
Rales	n	1,015		1,293			
	Abnormal	6	0.6	7	0.5	1.09 (0.38,3.15)	0.86
	Normal	1,009	99.4	1,286	99.5		
X Ray	n	1,012		1,289			
	Abnormal	102	10.1	149	11.6	0.86 (0.66,1.12)	0.26
	Normal	910	89.9	1,140	88.4		

TABLE 20-3.

Adjusted Analyses of Respiratory Variables by Group*

Variable	Group		Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks**
	Ranch Hand Total	Comparison Total			
Asthma	1,012	1,290	1.16 (0.76,1.75)	0.57	PACKYR (p=0.023) GRP*PACKYR (Borderline: p=0.068)
Bronchitis	1,011	1,290	0.97 (0.76,1.25)	0.83	None
Pleurisy	1,012	1,289	****	****	GRP*PACKYR (p=0.0026)
Pneumonia	1,012	1,289	1.02 (0.82,1.26)	0.93	AGE (p=0.0001)
Tuberculosis	1,011	1,290	****	****	GRP*PACKYR (p=0.034)
Thorax and Lungs	1,011	1,291	1.27 (0.87,1.84)	0.19	AGE (p<0.0001) PACKYR (p<0.001)
Asymmetrical Expiration	1,011	1,291	0.81 (0.14,4.85)	0.85	AGE*PACKYR (p=0.036)
Hyperresonance	1,011	1,291	1.04 (0.63,1.73)	0.80	AGE (p<0.0001) PACKYR (p<0.0001)
Dullness	1,011	1,291	2.56 (0.31,17.66)	0.47	None
Wheezes	1,011	1,291	1.46 (0.80,2.64)	0.22	PACKYR (p<0.0001)
Rales	1,011	1,291	****	****	GRP*AGE (p=0.046) GRP*PACKYR (Borderline: p=0.070) AGE*PACKYR (Borderline: p=0.090)
X Ray	1,008	1,287	0.85 (0.65,1.11)	0.22	AGE (p<0.0001) PACKYR (p=0.0019) GRP*PACKYR (Borderline: p=0.060)

*Group-by-covariate interactions are described in Table 20-4.

**Abbreviations

PACKYR: Lifetime smoking history (pack-years)
GRP: Group

****Group-by-covariate interaction--relative risk, confidence interval, and p-value not presented.

TABLE 20-4.

Summary of Group-by-Covariate Interactions for Respiratory Variables

Variable	Interaction	Stratification	Statistic	Group				Adj. Relative Risk (95% C.I.)	p-Value		
				Ranch Hand		Comparison					
				Number	Percent	Number	Percent				
Asthma	Group-by-Pack-Year	0	n	291		367		2.84 (1.00, 7.89)	0.05		
			Abnormal	11	3.78	5	1.36				
			Normal	280	96.22	362	98.64				
		>0-10	n	284		397				1.52 (0.75, 3.10)	0.25
			Abnormal	16	5.63	15	3.78				
			Normal	268	94.37	382	96.22				
		>10	n	437		526				0.67 (0.37, 1.23)	0.19
			Abnormal	17	3.89	30	5.70				
			Normal	420	96.11	496	94.30				
Pleurisy	Group-by-Pack-Year	0	n	291		366		1.27 (0.48, 3.32)	0.64		
			Abnormal	8	2.75	8	2.19				
			Normal	283	97.25	358	97.821				
		>0-10	n	284		397				3.29 (1.43, 7.49)	<0.001
			Abnormal	18	6.34	8	2.02				
			Normal	266	93.66	389	97.98				
		>10	n	437		526				0.60 (0.35, 1.02)	0.06
			Abnormal	21	4.81	41	7.79				
			Normal	416	95.19	485	92.21				

TABLE 20-4. (continued)

Summary of Group-by-Covariate Interactions for Respiratory Variables

Variable	Interaction	Stratification	Statistic	Group				Adj. Relative Risk (95% C.I.)	p-Value		
				Ranch Hand		Comparison					
				Number	Percent	Number	Percent				
Tubercu- losis	Group-by- Pack-Year	0	n	290		367		0.31 (0.06,2.26)	0.28		
			Abnormal	1	0.34	4	1.09				
			Normal	289	99.66	363	98.91				
		>0-10	n	284		397				--	0.02
			Abnormal	4	1.41	0	0.00				
			Normal	280	98.59	397	100.00				
		>10	n	437		526				1.20 (0.21,2.04)	0.86
			Abnormal	2	0.46	2	0.38				
			Normal	435	99.54	524	99.62				
Rales	Group-by- Age	>1942	n	384		509		1.33 (0.14,12.78)	0.84		
			Abnormal	1	0.26	1	0.20				
			Normal	383	99.74	508	99.80				
		1922-1942	n	600		741				1.03 (0.33,3.25)	0.96
			Abnormal	5	0.83	6	0.81				
			Normal	595	99.17	735	99.19				
		<1922	n	27		41				--	--
			Abnormal	0	0.00	0	0.00				
			Normal	27	100.00	41	100.00				

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TABLE 20-4. (continued)

Summary of Group-by-Covariate Interactions for Respiratory Variables

Variable	Interaction	Stratification	Statistic	Group				Adj. Relative Risk (95% C.I.)	p-Value		
				Ranch Hand		Comparison					
				Number	Percent	Number	Percent				
Rales	Group-by-Pack-Year	0	n	291		367		0.63 (0.09, 5.26)	0.71		
			Abnormal	1	0.34	2	0.54				
			Normal	290	99.66	365	99.46				
		>0-10	n	283		398				--	0.23
			Abnormal	0	0.00	2	0.50				
			Normal	283	100.00	396	99.50				
		>10	n	437		526				2.02 (0.51, 7.67)	0.33
			Abnormal	5	1.14	3	0.57				
			Normal	432	98.86	523	99.43				
X Ray	Group-by-Pack-Year	0	n	290		365		0.50 (0.27, 0.93)	0.03		
			Abnormal	15	5.17	36	9.86				
			Normal	275	94.83	329	90.14				
		>0-10	n	282		398				1.26 (0.74, 2.14)	0.39
			Abnormal	28	9.93	32	8.04				
			Normal	254	90.07	366	91.96				
		>10	n	436		524				0.86 (0.60, 1.23)	0.40
			Abnormal	59	13.53	81	15.46				
			Normal	377	86.47	443	84.54				

-- No abnormalities present in Comparison group.

TABLE 20-5.

Exposure Index Analysis Results for Officers
p-Values of Dependent Variable by Covariate Association^{a, b}

Variable	D*EXP	D*AGE	D*PACKYR	D*EXP *AGE	D*EXP *PACKYR	D*AGE *PACKYR	D*EXP* AGE*PACKYR	Overall			
								Abnormal	Total	Percent	
Asthma								16	380	4.2	
Bronchitis					0.08		0.009	52	380	13.7	
Pleurisy		0.02						16	380	4.2	
Pneumonia							0.04	75	380	19.7	
Tuberculosis	(No Analysis; Only 3 Abnormal)										
Thorax and Lungs	0.05		0.02			0.06		17	380	4.5	
Asymmetrical Exp.	(No Analysis; Only 2 Abnormal)										
Hyperresonance					0.07			9	380	2.4	
Dullness	(No Analysis; Only 2 Abnormal)										
Wheezes								5	380	1.3	
Rales	(No Analysis; Only 3 Abnormal)										
X Ray	0.09	0.01	0.06				0.08	34	380	8.9	

^aDependent variable indicated by D in column headings.

^bAbbreviations:

EXP: Exposure index.

PACKYR: Pack-years.

TABLE 20-6.

Exposure Index Analysis Results for Enlisted Flyers
p-Values of Dependent Variable by Covariate Association^a

Variable	D*EXP	D*AGE	D*PACKYR	D*EXP *AGE	D*EXP *PACKYR	D*AGE *PACKYR	D*EXP* AGE*PACKYR	Overall			
								Abnormal	Total	Percent	
Asthma		0.07						6	175	3.4	
Bronchitis							0.005	21	174	12.1	
Pleurisy							0.08	9	175	5.1	
Pneumonia				0.08				39	175	22.3	
Tuberculosis	(No Analysis; Only 2 Abnormal)										
Thorax and Lungs	0.04							19	175	10.9	
Asymmetrical Exp.	(No Analysis; 0 Abnormal)										
Hyperresonance	0.04				0.08			9	175	5.1	
Dullness	(No Analysis; 0 Abnormal)										
Wheezes								7	175	4.0	
Rales	(No Analysis; Only 1 Abnormal)										
X Ray	0.04							19	175	10.9	

^aDependent variable indicated by D in column headings.

TABLE 20-7.

Exposure Index Analysis Results for Enlisted Groundcrew:
p-Values of Dependent Variable by Covariate Association*

Variable	D*EXP	D*AGE	D*PACKYR	D*EXP* *AGE	D*EXP *PACKYR	D*AGE *PACKYR	D*EXP* AGE*PACKYR	Overall		
								Abnormal	Total	Percent
Asthma				0.08			0.02	22	457	4.8
Bronchitis	0.08							55	457	12.0
Pleurisy				0.03				22	457	4.8
Pneumonia			0.01					81	457	17.7
Tuberculosis	(No Analysis; Only 2 Abnormal)									
Thorax and Lungs		0.06						25	456	5.5
Asymmetrical Exp.	(No Analysis; 0 Abnormal)									
Hyperresonance		0.007						12	456	2.6
Dullness	(No Analysis; 0 Abnormal)									
Wheezes				0.009	0.02			12	456	2.6
Rales	(No Analysis; Only 2 Abnormal)									
X Ray		0.0005						49	456	10.8

*Dependent variable indicated by D in column headings.

Two sets of analyses were performed on enlisted groundcrew data. In the first set of analyses, all three year-of-birth categories (born after 1942, born between 1922 and 1942, born before 1922) were used. In the second set of analyses, only those born between 1922 and 1942 and after 1942 were used, since only one enlisted groundcrew Ranch Hand was born before 1922. All testing results in the two sets of analyses were the same, except for the asthma-by-age interaction shown in Table 20-6.

Each of the dependent variable-by-exposure category interactions are noted by occupation category in Appendix R, Tables R-4 through R-18. These data are considered too sparse for meaningful interpretation.

SUMMARY AND CONCLUSIONS

A summary of the results on the analyses of reported history of respiratory illness and of radiological and clinical findings is given in Table 20-8.

Based on the 31 December 1986 mortality data, there were seven deaths from respiratory conditions in the Comparison group and none in the Ranch Hand group.

TABLE 20-8.

Overall Summary Results of Unadjusted and
Adjusted Analyses of Pulmonary Disease

Pulmonary Disease	Unadjusted	Adjusted
<u>Reported History of Respiratory Illness</u>		
Asthma	NS	NS
Bronchitis	NS	NS
Pleurisy	NS	****
Pneumonia	NS	NS
Tuberculosis	NS	****
<u>Radiological and Clinical Findings</u>		
Thorax and Lungs	NS	NS
Asymmetrical Expiration	NS	NS
Hyperresonance	NS	NS
Dullness	NS	NS
Wheezes	NS	NS
Rales	NS	****
X Ray	NS	NS

NS: Not significant ($p > 0.10$)

****Group-by-covariate interaction.

There were no group differences found for reported history of asthma, bronchitis, pleurisy, or tuberculosis based on the unadjusted analyses. Adjustments for age and lifetime smoking did not alter the findings of group similarity, although there was a significant group-by-pack-year interaction for pleurisy and for tuberculosis.

Similarly, there were no significant group differences in the unadjusted analyses for the radiological and clinical respiratory findings of thorax and lungs, asymmetrical expiration, hyperresonance, dullness, wheezes, rales, and x-ray interpretations. These findings were supported by the adjusted analyses, although there was a group-by-age interaction for rales.

The exposure index analyses revealed no consistent dose-response pattern.

Analyses of past history of respiratory illness and the clinical and radiological examination of the chest and lungs did not reveal any statistically significant differences between the Ranch Hand and Comparison groups suggestive of herbicide related disease. Several group-by-covariate interactions did exhibit statistical significance, but these findings did not indicate any consistent patterns suggesting different disease experience in the two groups.

REFERENCES

CHAPTER 20

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