

7. BIRTH DEFECT SEVERITY

7.1 Introduction

All live births were categorized according to severity following the CDC definition [14]. Major defects were defined as those that potentially can affect survival, require substantial medical care, result in marked physical or psychological handicaps, or interfere with a child's prospects for a productive and fulfilling life. Minor defects were defined as those that are not associated with one or more of the above mentioned sequelae.

Analyses were first carried out with each of Models 1, 2 and 3 to assess changes in the association between severity and dioxin with time of conception relative to the father's duty in SEA (pre-SEA, post-SEA) without adjustment for covariates. In these analyses, severity was reduced to two levels (not major, major), where "not major" is defined as none or minor. All analyses were carried out without and then with restriction to full sibling children. These analyses are shown in Tables 7-1 through 7-6.

The significance of the association between severity and dioxin was also assessed among post-SEA children with each of the three models. Each analysis was first carried out with severity having 3 levels (none, minor, major) and then with severity categorized with two levels (not major, major). The 3-category analyses were carried out without adjustment for covariates. The 2-category analyses were carried out without and then with adjustment for covariates. All analyses were carried out without and with restriction to full siblings. These analyses are shown in Tables 7-7 through 7-18.

In this section, rates were computed as the number of occurrences of a birth defect of a given severity per 1000 children.

7.2 Pre-post SEA Exposure Analyses - All Children

Birth Defect Severity (2 Categories; All Children)

Model 1: Children of Ranch Hands - $\log_2(\text{Initial Dioxin})$

Without adjustment for covariates (Table 7-1 [a] and [b]), there is no significant variation in the association between birth defect severity (not major, major) and initial dioxin with time of conception among children of Ranch Hands with more than 10 ppt ($p=0.348$) or more than 5 ppt ($p=0.646$) current dioxin.

Table 7-1

Pre-Post SEA Counts and Rates of
Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
Restrictions: All Children of Ranch Hands
Model 1: $\text{Log}_2(\text{Initial Dioxin})$

Ranch Hands - $\text{Log}_2(\text{Initial Dioxin})$ - Unadjusted								
Exposure Restriction	Initial Dioxin	Time of Conception Relative to the Father's Duty in SEA						
		Pre-SEA			Post-SEA			p-Value
		n	Maj	Rate	n	Maj	Rate	
a) D>10 ppt (n=1208)	Low	249	8	32.1	106	6	56.6	0.348
	Medium	338	14	41.4	245	25	102.0	
	High	113	5	44.2	157	10	63.7	
b) D>5 ppt (n=1748)	Low	286	9	31.5	155	9	58.1	0.646
	Medium	616	19	30.8	308	26	84.4	
	High	156	10	64.1	227	15	66.1	

Birth Defect Severity (2 Categories, All Children)

Model 2: Children of Ranch Hands - $\text{Log}_2(\text{Current Dioxin})$ and Time

Without adjustment for covariates (Table 7-2 [a] and [b]), there is no significant variation in the association between birth defect severity (not major, major) and current dioxin with time since duty in SEA and time of conception among children of Ranch Hands with more than 10 ppt ($p=0.506$) or more than 5 ppt ($p=0.964$) current dioxin.

Table 7-2

**Pre-Post SEA Counts and Rates of
Birth Defect Severity (Not Major, Major)**

Variable: Birth Defect Severity (Not Major, Major)
Restrictions: All Children of Ranch Hands
Model 2: $\text{Log}_2(\text{Current Dioxin})$, Time

Ranch Hands - $\text{Log}_2(\text{Current Dioxin})$, Time - Unadjusted						
Exposure Restriction	Time of Conception	Time Since SEA (years)	Severity Rate (No./n) Current Dioxin			p-Value
			Low	Medium	High	
a) D>10 ppt (n=1210)	Pre-SEA	≤18.6	36.5 (5/137)	43.7 (8/183)	81.1 (3/37)	0.506
		>18.6	21.1 (2/95)	35.1 (6/171)	38.5 (3/78)	
	Post-SEA	≤18.6	48.4 (3/62)	111.9 (15/134)	41.7 (3/72)	
		>18.6	75.0 (3/40)	101.9 (11/108)	75.3 (7/93)	
b) D>5 ppt (n=1748)	Pre-SEA	≤18.6	25.5 (4/157)	44.7 (14/313)	45.5 (3/66)	0.964
		>18.6	26.7 (4/150)	33.3 (9/270)	39.2 (4/102)	
	Post-SEA	≤18.6	55.6 (5/90)	92.0 (16/174)	54.5 (6/110)	
		>18.6	15.9 (1/63)	110.3 (15/136)	59.8 (7/117)	

Birth Defect Severity (2 Categories; All Children)

Model 3: Children of Ranch Hands and Comparisons - Categorized Current Dioxin

Without adjustment for covariates (Table 7-3), there is no significant variation in the overall association between birth defect severity (not major, major) and categorized current dioxin with time of conception ($p=0.203$). However, the association between birth defect severity and time of conception among children of Ranch Hands in the Low ($p=0.038$) category is significantly different from the association among children of Comparisons in the Background category. This finding is caused by a high rate of major severity (126.4 per 1000) among post-SEA children of Ranch Hands in the Low category relative to that of children of Comparisons in the Background category (57.1 per 1000). The association between birth defect severity and time of birth among children of Ranch Hands in the High ($p=0.984$) and Unknown ($p=0.529$) categories are not significantly different from the association among children of Comparisons in the Background category.

Table 7-3

Pre-Post SEA Counts and Rates of Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
 Restrictions: All Children of Ranch Hands and Comparisons
 Model 3: Categorized Current Dioxin

Exposure Category	n	Pre-SEA		Post-SEA			Odds Ratio	Category Contrast	p-Value
		Maj	Rate	n	Maj	Rate			
Background	1459	60	41.1	981	56	57.1	1.41	All Exp Categ	0.203
Unknown	582	20	34.4	282	17	60.3	1.80	Unk vs Bkgd	0.529
Low	290	12	41.4	174	22	126.4	3.35	Low vs Bkgd	0.038
High	168	7	41.7	227	13	57.3	1.40	High vs Bkgd	0.984
Total	2499			1664					

7.3 Pre-post SEA Exposure Analyses - Full Siblings

Birth Defect Severity (2 Categories; Full Siblings)

Model 1: Children of Ranch Hands - Log₂(Initial Dioxin)

Without adjustment for covariates (Table 7-4 [a] and [b]), there is no significant variation in the association between birth defect severity (not major, major) and initial dioxin with time of conception among full sibling children of Ranch Hands with more than 10 ppt (p=0.481) or more than 5 ppt (p=0.593) current dioxin.

Table 7-4

Pre-Post SEA Counts and Rates of Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
 Restrictions: Full Siblings of Ranch Hands
 Model 1: Log₂(Initial Dioxin)

Ranch Hands - Log ₂ (Initial Dioxin) - Unadjusted								
		Time of Conception Relative to the Father's Duty in SEA						
Exposure Restriction	Initial Dioxin	n	Pre-SEA		Post-SEA			p-Value
			Maj	Rate	n	Maj	Rate	
a) D>10 ppt (n=1030)	Low	231	8	34.6	78	3	38.5	0.481
	Medium	276	11	39.9	206	19	92.2	
	High	103	5	48.5	136	7	51.5	
b) D>5 ppt (n=1489)	Low	252	9	35.7	114	7	61.4	0.593
	Medium	545	18	33.0	245	18	73.5	
	High	135	8	59.3	198	12	60.6	

Birth Defect Severity (2 Categories; Full Siblings)

Model 2: Children of Ranch Hands - Log₂(Current Dioxin) and Time

Without adjustment for covariates (Table 7-5 [a] and [b]), there is no significant variation in the association between birth defect severity (not major, major) and current dioxin with time since duty in SEA and time of conception among full sibling children of Ranch Hands with more than 10 ppt (p=0.423) or more than 5 ppt (p=0.985) current dioxin.

Table 7-5

Pre-Post SEA Counts and Rates of
Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
Restrictions: Full Siblings of Ranch Hands
Model 2: $\text{Log}_2(\text{Current Dioxin})$, Time

Ranch Hands - $\text{Log}_2(\text{Current Dioxin})$, Time - Unadjusted						
Exposure Restriction	Time of Conception	Time Since SEA (years)	Severity Rate (No./n) Current Dioxin			p-Value
			Low	Medium	High	
a) D>10 ppt (n=1032)	Pre-SEA	≤18.6	40.3 (5/124)	45.2 (7/155)	85.7 (3/35)	0.423
		>18.6	23.5 (2/85)	28.0 (4/143)	43.5 (3/69)	
	Post-SEA	≤18.6	42.6 (2/47)	95.7 (11/115)	46.9 (3/64)	
		>18.6	35.7 (1/28)	97.8 (9/92)	53.3 (4/75)	
b) D>5 ppt (n=1489)	Pre-SEA	≤18.6	31.7 (4/126)	47.1 (13/276)	50.0 (3/60)	0.985
		>18.6	27.6 (4/145)	29.5 (7/237)	45.5 (4/88)	
	Post-SEA	≤18.6	67.8 (4/59)	83.3 (12/144)	51.0 (5/98)	
		>18.6	18.9 (1/53)	103.8 (11/106)	41.2 (4/97)	

Birth Defect Severity (2 Categories; Full Siblings)

Model 3: Children of Ranch Hands and Comparisons - Categorized Current Dioxin

Without adjustment for covariates (Table 7-6), there is no significant variation in the overall association between birth defect severity (not major, major) and categorized current dioxin with time of conception ($p=0.106$) among full siblings. However, the association between birth defect severity and time of conception among children of Ranch Hands in the Low category is significantly different from the association among children of Comparisons in the Background category ($p=0.030$). This finding is caused by a high rate of major severity (121.6 per 1000) among post-SEA children of Ranch Hands in the Low category relative to that of children of Comparisons in the Background category (56.7 per 1000). The associations between birth defect severity and time of conception among children of Ranch Hands in the High ($p=0.600$) and Unknown ($p=0.332$) categories are not significantly different from the association among children of Comparisons in the Background category.

Table 7-6

Pre-Post SEA Counts and Rates of Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
 Restrictions: Full Siblings of Ranch Hands and Comparisons
 Model 3: Categorized Current Dioxin

Exposure Category	n	Pre-SEA		Post-SEA		Odds Ratio	Category Contrast	p-Value	
		Maj	Rate	n	Maj				Rate
Background	1250	55	44.0	812	46	56.7	1.30	All Exp Categ	0.106
Unknown	514	20	38.9	221	16	72.4	1.93	Unk vs Bkgd	0.332
Low	244	9	36.9	148	18	121.6	3.62	Low vs Bkgd	0.030
High	148	7	47.3	195	9	46.2	0.97	High vs Bkgd	0.600
Total	2156			1376					

7.4 Post-SEA Exposure Analyses - All Children

Birth Defect Severity (3 Categories; All Children)

Model 1: Children of Ranch Hands - Log₂(Initial Dioxin)

Without adjustment for covariates (Table 7-7 [a] and [b]), there is no association between birth defect severity (none, minor, major) and initial dioxin among children of Ranch Hands having more than 10 ppt (p=0.252) or more than 5 ppt (p=0.828) current dioxin.

Table 7-7

Post-SEA Counts and Rates of Birth Defect Severity (None, Minor, Major)

Variable: Birth Defect Severity (None, Minor, Major)
 Restrictions: All Children of Ranch Hands
 Children Conceived during or after the
 Father's Duty in SEA
 Model 1: Log₂(Initial Dioxin)

Ranch Hands - Log ₂ (Initial Dioxin) - Unadjusted						
Exposure Restriction	Initial Dioxin	n	Rate (count)			p-Value
			Severity Index Level	None	Minor	
a) D>10 ppt	Low	106	811.3 (86)	132.1 (14)	56.6 (6)	0.252
	Medium	245	722.4 (177)	175.5 (43)	102.0 (25)	
	High	157	802.5 (126)	133.8 (21)	63.7 (10)	
b) D>5 ppt	Low	155	774.2 (120)	167.7 (26)	58.1 (9)	0.828
	Medium	308	766.2 (236)	149.4 (46)	84.4 (26)	
	High	227	784.1 (178)	149.8 (34)	66.1 (15)	

Birth Defect Severity (2 Categories; All Children)

Model 1: Children of Ranch Hands - Log₂(Initial Dioxin)

Without adjustment for covariates (Table 7-8 [a] and [b]), there is no association between birth defect severity (not major, major) and initial dioxin among children of Ranch Hands with more than 10 ppt (p=0.585) or more than 5 ppt (p=0.568) current dioxin.

After adjustment for covariates (Table 7-8 [c] and [d]), there is no association between birth defect severity and initial dioxin among children of Ranch Hands having more than 10 ppt (p=0.868) or more than 5 ppt (p=0.418) current dioxin.

Table 7-8

**Post-SEA Counts and Rates of
Birth Defect Severity (Not Major, Major)**

Variable: Birth Defect Severity (Not Major, Major)
 Restrictions: All Children of Ranch Hands
 Children Conceived during or after the
 Father's Duty in SEA
 Model 1: Log₂(Initial Dioxin)

Ranch Hands - Log₂(Initial Dioxin) - Unadjusted					
Exposure Restriction	Initial Dioxin	n	Major Rate (n)	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=508)	Low	106	56.6(6)	0.93(0.70,1.22)	0.585
	Medium	245	102.0(25)		
	High	157	63.7(10)		
b) D>5 ppt (n=690)	Low	155	58.1(9)	1.06(0.87,1.30)	0.568
	Medium	308	84.4(26)		
	High	227	66.1(15)		

Table 7-8 (Continued)

Ranch Hands - Log₂(Initial Dioxin) - Adjusted

Exposure Restriction	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=458)	1.02(0.77,1.37)	0.868	SMOKE(p=0.024)
d) D>5 ppt (n=616)	1.09(0.88,1.35)	0.418	RACE(p=0.097) SMOKE(p=0.048) OCC(p=0.074)

Birth Defect Severity (3 Categories; All Children)

Model 2: Children of Ranch Hands - Log₂(Current Dioxin) and Time

Without adjustment for covariates (Table 7-9 [a]), there is no significant variation in the association between birth defect severity (none, minor, major) and current dioxin with time since duty in SEA among children of Ranch Hands with more than 10 ppt current dioxin (p=0.616). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late (p=0.290) or early (p=0.798) tours.

Without adjustment for covariates (Table 7-9 [b]), there is no significant variation in the association between birth defect severity and current dioxin with time since duty in SEA among children of Ranch Hands with more than 5 ppt current dioxin (p=0.204). There is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late tours (p=0.535). However, there is a significant association between birth defect severity and current dioxin among children of Ranch Hands with early tours (p=0.032). The rate of minor birth defects among children of Ranch Hands in the medium dioxin category (169.1 per 1000) is greater than that of children of Ranch Hands in the low (79.4 per 1000) or high (119.7 per 1000) dioxin categories.

Table 7-9

Post-SEA Counts and Rates of
Birth Defect Severity (None, Minor, Major)

Variable: Birth Defect Severity (None, Minor, Major)
Restrictions: All Children of Ranch Hands
Children Conceived during or after the
Father's Duty in SEA
Model 2: $\text{Log}_2(\text{Current Dioxin}), \text{Time}$

Ranch Hands - $\text{Log}_2(\text{Current Dioxin}), \text{Time}$ - Unadjusted							
Exposure Restriction	Time Since SEA (years)	Exposure Category	n	Rate (Count)			p-Value
				Severity Index None	Severity Index Minor	Severity Index Major	
a) D>10 ppt (n=509)							0.616
	≤18.6	Low	62	806.5 (50)	145.2 (9)	48.4 (3)	0.290
		Medium	134	746.3 (100)	141.8 (19)	111.9 (15)	
		High	72	763.9 (55)	194.4 (14)	41.7 (3)	
	>18.6	Low	40	725.0 (29)	200.0 (8)	75.0 (3)	0.798
		Medium	108	750.0 (81)	148.1 (16)	101.9 (11)	
		High	93	795.7 (74)	129.0 (12)	75.3 (7)	

Table 7-9 (Continued)

Exposure Restriction	Time Since SEA (years)	Exposure Category	n	Rate (count)			p-Value
				Severity Index Level None	Minor	Major	
b) D>5 ppt (n=690)							0.204
	≤18.6	Low	90	733.3 (66)	211.1 (19)	55.6 (5)	0.535
		Medium	174	747.1 (130)	160.9 (28)	92.0 (16)	
		High	110	790.9 (87)	154.5 (17)	54.5 (6)	
	>18.6	Low	63	904.8 (57)	79.4 (5)	15.9 (1)	0.032
		Medium	136	720.6 (98)	169.1 (23)	110.3 (15)	
		High	117	820.5 (96)	119.7 (14)	59.8 (7)	

Birth Defect Severity (2 Categories; All Children)

Model 2: Children of Ranch Hands - \log_2 (Current Dioxin) and Time

Without adjustment for covariates (Table 7-10 [a]), there is no significant variation in the association between birth defect severity (not major, major) and current dioxin with time since duty in SEA among children of Ranch Hands having more than 10 ppt current dioxin ($p=0.703$). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late ($p=0.789$) or early ($p=0.784$) tours.

Without adjustment for covariates (Table 7-10 [b]), there is no significant variation in the association between birth defect severity (not major, major) and current dioxin with time since duty in SEA among children of Ranch Hands having more than 5 ppt current dioxin ($p=0.976$). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands late ($p=0.621$) or early ($p=0.576$) tours.

After adjustment for covariates (Table 7-10 [c]), there is significant variation in the association between birth defect severity (not major, major) and current dioxin with time since duty in SEA and the father's military occupation among children of Ranch Hands having more than 10 ppt current dioxin ($p=0.050$). The basis for this significance is displayed in Appendix Table E-1. After stratification, there is no significant change in the association between birth defect severity and current dioxin with time since duty in SEA for any of the three military occupations. Additionally, for no occupational stratum is there a significant association between birth defect severity and current dioxin among children of Ranch Hands with late or early tours.

If the above interaction is ignored, there is no significant change in association between birth defects severity and current dioxin with time since duty in SEA ($p=0.682$). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands late ($p=0.933$) or early ($p=0.576$) tours.

After adjustment for covariates (Table 7-10 [d]), there is no significant variation in the association between birth defect severity (not major, major), current dioxin level and time since duty in SEA among children of Ranch Hands having more than 10 ppt current dioxin ($p=0.807$). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late ($p=0.748$) or early ($p=0.457$) tours.

Table 7-10

Post-SEA Counts and Rates of
Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
Restrictions: All Children of Ranch Hands
Children Conceived during or after the
Father's Duty in SEA
Model 2: $\text{Log}_2(\text{Current Dioxin}), \text{Time}$

Ranch Hands - $\text{Log}_2(\text{Current Dioxin}), \text{Time}$ - Unadjusted						
Exposure Restriction	Time Since SEA (years)	Major Rate (No./n) Current Dioxin			Est. Relative Risk (95% C.I.)	p-Value
		Low	Medium	High		
a) D>10 ppt (n=509)						0.703
	≤18.6	48.4 (3/62)	111.9 (15/134)	41.7 (3/72)	0.94(0.61,1.45)	0.789
	>18.6	75.0 (3/40)	101.9 (11/108)	75.3 (7/93)	1.05(0.72,1.54)	0.784
b) D>5 ppt (n=690)						0.976
	≤18.6	55.6 (5/90)	92.0 (16/174)	54.5 (6/110)	1.08(0.80,1.46)	0.621
	>18.6	15.9 (1/63)	110.3 (15/136)	59.8 (7/117)	1.08(0.81,1.44)	0.576

Table 7-10 (Continued)

Ranch Hands - Log₂(Current Dioxin), Time - Adjusted

Exposure Restriction	Time Since SEA (years)	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=459)			0.682***	OCC*TIME*DIOXIN (p=0.050)
	≤18.6	1.02(0.63,1.66)***	0.933***	SMOKE(p=0.025)
	>18.6	0.90(0.62,1.31)***	0.576***	
d) D>5 ppt (n=616)			0.807	RACE(p=0.098) SMOKE(p=0.048)
	≤18.6	1.06(0.76,1.47)	0.748	OCC(p=0.070)
	>18.6	1.12(0.84,1.49)	0.457	

Birth Defect Severity (3 Categories; All Children)

Model 3: Children of Ranch Hands and Comparisons - Categorized Current Dioxin

Without adjustment for covariates (Table 7-11 [a]), there is a significant overall association between birth defect severity (none, minor, major) and categorized current dioxin (p=0.033). The distribution of severity among children of Ranch Hands in the Low category is significantly different from that of children of Comparisons in the Background category (p=0.002). This finding is caused by a high rate of major severity in children of Ranch Hands in the Low dioxin category (126.4 per 1000) relative to that of Comparisons in the Background category (57.1 per 1000). However, the distributions of birth defect severity among children of Ranch Hands in the High (p=0.860) and Unknown (p=0.919) categories are not significantly different from that of children of Comparisons in the Background category.

Table 7-11

Post-SEA Counts and Rates of
Birth Defect Severity (None, Minor, Major)

Variable: Birth Defect Severity (None, Minor, Major)
Restrictions: All Children of Ranch Hands and Comparisons
Children Conceived during or after the
Father's Duty in SEA
Model 3: Categorized Current Dioxin

a) Unadjusted

Exposure Category	n	Rate (n)			Category Contrast	p-Value
		Severity Index None	Minor	Level Major		
Background	981	792.0 (777)	150.9 (148)	57.1 (56)	All Exp Categ	0.033
Unknown	282	797.9 (225)	141.8 (40)	60.3 (17)	Unk vs Bkgd	0.919
Low	174	706.9 (123)	166.7 (29)	126.4 (22)	Low vs Bkgd	0.002
High	227	806.2 (183)	136.6 (31)	57.3 (13)	High vs Bkgd	0.860

Birth Defect Severity (2 Categories; All Children)

Model 3: Children of Ranch Hands and Comparisons - Categorized Current Dioxin

Without adjustment for covariates (Table 7-12 [a]), there is a significant overall association between birth defect severity (not major, major) and categorized current dioxin ($p=0.018$). The rate of major birth defects among children of Ranch Hands in the Low current dioxin category (126.4 per 1000) is significantly greater than the rate among children of Comparisons in the Background category, 57.1 per 1000 ($p=0.001$). The rates of major birth defects among children of Ranch Hands in the High ($p=0.991$) and Unknown ($p=0.839$) categories are not significantly different from that in children of Comparisons in the Background category.

After adjustment for covariates (Table 7-12 [b]), there is significant variation in the overall association between birth defect severity (not major, major) and categorized current dioxin with the mother's smoking (p=0.008) and also with the father's military occupation (p=0.027). The basis for this significance is displayed in Appendix Table E-1. There is a significant increase (p=0.005) in the rate of major birth defects among children of Ranch Hands in the Low category (233.3 per 1000) relative to the rate among children of Comparisons in the Background category whose mother who smoked during pregnancy and whose father was in the enlisted ground occupational category (48.5 per 1000). Among children whose mother did not smoke and whose father was an enlisted flyer, the rate of major birth defects among children of Ranch Hands in the Unknown category (266.7 per 1000) was significantly greater (p=0.023) than the rate in children of Comparisons in the Background category (52.6 per 1000). For many other strata there was insufficient data to assess the significance of these associations.

Table 7-12

Post-SEA Counts and Rates of
Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
Restrictions: All Children of Ranch Hands and Comparisons
Children Conceived during or after the
Father's Duty in SEA
Model 3: Categorized Current Dioxin

a) Unadjusted

Exposure Category	n	Major Count	Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	981	56	57.1	All Exp Categ		0.018
Unknown	282	17	60.3	Unk vs Bkgd	1.06(0.60,1.86)	0.839
Low	174	22	126.4	Low vs Bkgd	2.39(1.42(4.03)	0.001
High	227	13	57.3	High vs Bkgd	1.00(0.54,1.87)	0.991
Total	1664					

Table 7-12 (Continued)

b) Adjusted

Exposure Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	843	All Exp Categ		****	DRINK(p=0.035)
Unknown	246	Unk vs Bkgd	****	****	F-AGE(p=0.021)
Low	156	Low vs Bkgd	****	****	SMOKE*DIOXIN
High	203	High vs Bkgd	****	****	(p=0.008)
Total	1448				OCC*DIOXIN (p=0.027)

7.5 Post-SEA Exposure Analyses - Full Siblings

Birth Defect Severity (3 Categories; Full Siblings)

Model 1: Children of Ranch Hands - Log_2 (Initial Dioxin)

Without adjustment for covariates (Table 7-13 [a] and [b]), there is no association between birth defect severity (none, minor, major) and initial dioxin among full sibling children of Ranch Hands with more than 10 ppt (p=0.315) or more than 5 ppt (p=0.717) current dioxin.

Table 7-13

Post-SEA Counts and Rates of
Birth Defect Severity (None, Minor, Major)

Variable: Birth Defect Severity (None, Minor, Major)
Restrictions: Full Siblings of Ranch Hands
Children Conceived during or after the
Father's Duty in SEA
Model 1: $\text{Log}_2(\text{Initial Dioxin})$

Ranch Hands - $\text{Log}_2(\text{Initial Dioxin})$ - Unadjusted						
Exposure Restriction	Initial Dioxin	n	Rate (count)			p-Value
			Severity None	Index Minor	Level Major	
a) D>10 ppt	Low	78	794.9 (62)	166.7 (13)	38.5 (3)	0.315
	Medium	206	723.3 (149)	184.5 (38)	92.2 (19)	
	High	136	801.5 (109)	147.1 (20)	51.5 (7)	
b) D>5 ppt	Low	114	824.6 (94)	114.0 (13)	61.4 (7)	0.717
	Medium	245	763.3 (187)	163.3 (40)	73.5 (18)	
	High	198	777.8 (154)	161.6 (32)	60.6 (12)	

Birth Defect Severity (2 Categories; Full Siblings)

Model 1: Children of Ranch Hands - $\text{Log}_2(\text{Initial Dioxin})$

Without adjustment for covariates (Table 7-14 [a] and [b]), there is no significant association between birth defect severity (not major, major) and initial dioxin among full sibling children of Ranch Hands with more than 10 ppt (p=0.770) or more than 5 ppt (p=0.941) current dioxin.

After adjustment for covariates (Table 7-14 [c]), there is no significant association between birth defect severity and initial dioxin among full sibling children of Ranch Hands with more than 10 ppt current dioxin (p=0.919).

After adjustment for covariates (Table 7-14 [d]), there is no significant association between birth defect severity and initial dioxin among full sibling children of Ranch Hands with more than 5 ppt current dioxin (p=0.970).

Table 7-14

Post-SEA Counts and Rates of
Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
Restrictions: Full Siblings of Ranch Hands
Children Conceived during or after the
Father's Duty in SEA
Model 1: $\text{Log}_2(\text{Initial Dioxin})$

Ranch Hands - $\text{Log}_2(\text{Initial Dioxin})$ - Unadjusted						
Exposure Restriction	Initial Dioxin	n	Major Count Rate		Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=420)	Low	78	3	38.5	0.95(0.69,1.32)	0.770
	Medium	206	19	92.2		
	High	136	7	51.5		
b) D>5 ppt (n=557)	Low	114	7	61.4	1.01(0.80,1.28)	0.941
	Medium	245	18	73.5		
	High	198	12	60.6		
Ranch Hands - $\text{Log}_2(\text{Initial Dioxin})$ - Adjusted						
Exposure Restriction	Adj. Relative Risk (95% C.I.)		p-Value		Covariate Remarks	
c) D>10 ppt (n=390)	1.02(0.73,1.42)		0.919		DRINK(p=0.085) SMOKE(p=0.012)	
d) D>5 ppt (n=513)	1.01(0.79,1.28)		0.970		SMOKE(p=0.055)	

Birth Defect Severity (3 Categories; Full Siblings)

Model 2: Children of Ranch Hands - \log_2 (Current Dioxin) and Time

Without adjustment for covariates (Table 7-15 [a]), there is no significant variation in the association between birth defect severity (none, minor, major) and current dioxin with time since duty in SEA among full sibling children of Ranch Hands with more than 10 ppt current dioxin ($p=0.679$). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late ($p=0.442$) or early ($p=0.430$) tours.

Without adjustment for covariates (Table 7-15 [b]), there is no significant variation in the association between birth defect severity and current dioxin with time since duty in SEA among full sibling children of Ranch Hands with more than 5 ppt current dioxin ($p=0.415$). There is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late tours ($p=0.794$). However, there is a significant association between birth defect severity and current dioxin among children of Ranch Hands with early tours ($p=0.016$). This finding is caused by the high rate of major defects in children of Ranch Hands with medium current dioxin levels (103.8 per 1000) and the low rates in children of Ranch Hands with low current dioxin levels (18.9 per 1000).

Table 7-15

Post-SEA Counts and Rates of
Birth Defect Severity (None, Minor, Major)

Variable: Birth Defect Severity (None, Minor, Major)
Restrictions: Full Siblings of Ranch Hands
Children Conceived during or after the
Father's Duty in SEA
Model 2: $\text{Log}_2(\text{Current Dioxin}), \text{Time}$

Ranch Hands - $\text{Log}_2(\text{Current Dioxin}), \text{Time}$ - Unadjusted							
Exposure Restriction	Time Since SEA (years)	Current Dioxin	n	Rate (count)			p-Value
				Severity Index None	Minor	Major	
a) D>10 ppt (n=421)							0.679
	≤18.6	Low	47	766.0 (36)	191.5 (9)	42.6 (2)	0.442
		Medium	115	765.2 (88)	139.1 (16)	95.7 (11)	
		High	64	734.4 (47)	218.8 (14)	46.9 (3)	
	>18.6	Low	28	714.3 (20)	250.0 (7)	35.7 (1)	0.430
		Medium	92	739.1 (68)	163.0 (15)	97.8 (9)	
		High	75	813.3 (61)	133.3 (10)	53.3 (4)	

Table 7-15 (Continued)

Ranch Hands - Log₂(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time Since SEA (years)	Current Dioxin	n	Rate (count)			p-Value
				Severity	Index	Level	
				None	Minor	Major	
b) D>5 ppt (n=557)							0.415
	≤18.6	Low	59	796.6 (47)	135.6 (8)	67.8 (4)	0.794
		Medium	144	736.1 (106)	180.6 (26)	83.3 (12)	
		High	98	785.7 (77)	163.3 (16)	51.0 (5)	
	>18.6	Low	53	924.5 (49)	56.6 (3)	18.9 (1)	0.016
		Medium	106	707.5 (75)	188.7 (20)	103.8 (11)	
		High	97	835.1 (81)	123.7 (12)	41.2 (4)	

Birth Defect Severity (2 Categories; Full Siblings)

Model 2: Children of Ranch Hands - Log₂(Current Dioxin) and Time

Without adjustment for covariates (Table 7-16 [a]), there is no significant variation in the association between birth defect severity (not major, major) and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 10 ppt current dioxin (p=0.688). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late (p=0.860) or early (p=0.446) tours.

Without adjustment for covariates (Table 7-16 [b]), there is no significant variation in the association between birth defect severity (not major, major) and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 5 ppt current dioxin (p=0.899). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late (p=0.948) or early (p=0.804) tours.

After adjustment for covariates (Table 7-16 [c]), there is no significant variation in the association between birth defect severity (not major, major) and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 10 ppt current dioxin (p=0.755). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late (p=0.992) or early (p=0.651) tours.

After adjustment for covariates (Table 7-16 [d]), there is no significant variation in the association between birth defect severity (not major, major) and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 5 ppt current dioxin (p=0.853). Furthermore, there is no significant association between birth defect severity and current dioxin among children of Ranch Hands with late (p=0.971) or early (p=0.818) tours.

Table 7-16

Post-SEA Counts and Rates of
Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
Restrictions: Full Siblings of Ranch Hands
Children Conceived during or after the
Father's Duty in SEA
Model 2: $\text{Log}_2(\text{Current Dioxin}), \text{Time}$

Ranch Hands - $\text{Log}_2(\text{Current Dioxin}), \text{Time}$ - Unadjusted						
Exposure Restriction	Time Since SEA (years)	Major Rate (No./n) Current Dioxin			Est. Relative Risk (95% C.I.)	p-Value
		Low	Medium	High		
a) D>10 ppt (n=421)						0.688
	≤18.6	42.6 (2/47)	95.7 (11/115)	46.9 (3/64)	0.96(0.59,1.56)	0.860
	>18.6	35.7 (1/28)	97.8 (9/92)	53.3 (4/75)	0.83(0.52,1.33)	0.446
b) D>5 ppt (n=557)						0.899
	≤18.6	67.8 (4/59)	83.3 (12/144)	51.0 (5/98)	1.01(0.72,1.43)	0.948
	>18.6	18.9 (1/53)	103.8 (11/106)	41.2 (4/97)	1.04(0.74,1.46)	0.804

Table 7-16 (Continued)

Ranch Hands - Log₂(Current Dioxin), Time - Adjusted

Exposure Restriction	Time Since SEA (years)	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=391)			0.755	SMOKE(p=0.020)
	≤18.6	1.00(0.60,1.67)	0.992	
	>18.6	0.90(0.57,1.42)	0.651	
d) D>5 ppt (n=513)			0.853	SMOKE(p=0.052)
	≤18.6	0.99(0.70,1.42)	0.971	
	>18.6	1.04(0.74,1.45)	0.818	

Birth Defect Severity (3 Categories, Full Siblings)

Model 3: Children of Ranch Hands and Comparisons - Categorized Current Dioxin

Without adjustment for covariates (Table 7-17 [a]), there is a significant overall association between birth defect severity (none, minor, major) and categorized current dioxin (p=0.028) among full siblings. There is a significant difference between the rates of birth defect severity among children of Ranch Hands in the Low category (p=0.010) and no significant differences between the rates among children of Ranch Hands in the Unknown (p=0.200) and High (p=0.727) categories with the rate in children of Comparisons in the Background category. Among children of Ranch Hands in the Low category, the rate of major defects (121.6 per 1000) is greater than that in Comparison children (56.7 per 1000) and the rates of minor birth defects are nearly equal in the two groups (175.7 versus 157.6 per 1000).

Table 7-17

Post-SEA Counts and Rates of
Birth Defect Severity (None, Minor, Major)

Variable: Birth Defect Severity (None, Minor, Major)
Restrictions: Full Siblings of Ranch Hands and Comparisons
Children Conceived during or after the
Father's Duty in SEA
Model 3: Categorized Current Dioxin

a) Unadjusted

Dioxin Category	n	Rate (count)			Category Contrast	p-Value
		Severity Index Level None	Minor	Major		
Background	812	785.7 (638)	157.6 (128)	56.7 (46)	All Exp Categ	0.028
Unknown	221	814.5 (180)	113.1 (25)	72.4 (16)	Unk vs Bkgd	0.200
Low	148	702.7 (104)	175.7 (26)	121.6 (18)	Low vs Bkgd	0.010
High	195	810.3 (158)	143.6 (28)	46.2 (9)	High vs Bkgd	0.727

Birth Defect Severity (2 Categories; Full Siblings)

Model 3: Children of Ranch Hands and Comparisons - Categorized Current Dioxin

Without adjustment for covariates (Table 7-18 [a]), there is a significant overall association between birth defect severity (not major, major) and categorized current dioxin ($p=0.033$) among full siblings. The rate of major birth defects among children of Ranch Hands in Low category (121.6 per 1000) is significantly greater ($p=0.005$) than that in children of Comparisons in the Background category (56.7 per 1000). The rates in major birth defects among children of Ranch Hands in the High ($p=0.563$) and Unknown ($p=0.383$) categories are not significantly different from that of children of Comparisons in the Background category.

After adjustment for covariates (Table 7-18 [b]), there is significant variation in the overall association between birth defect severity (not major, major) and categorized current dioxin with the mother's smoking during pregnancy ($p=0.016$) among full siblings. The basis for this variation is shown in Appendix Table E-1. There is a significant overall association between birth defect severity (not major, major) and categorized current dioxin in children whose mother smoked during pregnancy ($p=0.014$), while there was no significant association in children whose mother did not smoke during pregnancy ($p=0.229$). Furthermore, among children whose mother smoked, the rate of major birth defects in children of Ranch Hands in the Low category (235.3 per 1000) is significantly greater than that in children of Comparisons in the Background category (39.7 per 1000), $p=0.004$. The rates in the High ($p=0.308$) and the Unknown ($p=0.513$) categories are not significantly different from that in the Background category.

Table 7-18

Post-SEA Counts and Rates of
Birth Defect Severity (Not Major, Major)

Variable: Birth Defect Severity (Not Major, Major)
Restrictions: Full Siblings of Ranch Hands and Comparisons
Children Conceived during or after the
Father's Duty in SEA
Model 3: Categorized Current Dioxin

a) Unadjusted

Dioxin Category	n	Major Rate (No.)	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	812	56.7(46)	All Exp Categ		0.033
Unknown	221	72.4(16)	Unk vs Bkgd	1.30(0.72, 2.34)	0.383
Low	148	121.6(18)	Low vs Bkgd	2.31(1.30, 4.10)	0.005
High	195	46.2(9)	High vs Bkgd	0.81(0.39, 1.68)	0.563
Total	1376				

Table 7-18 (Continued)

b) Adjusted

Dioxin Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	715	All Exp Categ		0.059***	RACE(p=0.069)
Unknown	199	Unk vs Bkgd	1.31(0.72,2.37)***	0.381***	DRINK(p=0.009)
Low	137	Low vs Bkgd	2.11(1.16,3.82)***	0.014***	M-AGE(p=0.053)
High	180	High vs Bkgd	0.75(0.36,1.58)***	0.452***	F-AGE(p=0.060) C-TIME(p=0.079)
Total	1231				SMOKE*DIOXIN (p=0.016)

7.6 Conclusion

Throughout this section, nonsignificant results are indicated by NS, borderline significant results are indicated by NS* and the presence of interactions with the p-value greater than or equal to 0.01 and less than 0.05 are indicated with a preceding double asterisk (**). Four asterisks (****) represent the presence of an interaction between a covariate and dioxin with a p-value less than 0.01. The p-value is replaced by a double hyphen (--) when the analysis was not carried out due to sparse data.

All live births were assigned to one of three birth defect severity categories (none, minor, major) according to standardized definitions and medical record review. The significance of the association between birth defect severity and the father's dioxin level was assessed with Models 1, 2 and 3 under various combinations of constraints on severity, sibship and statistical adjustment.

Pre-post SEA analyses were carried out with severity reduced to two categories (major, not major) and unadjusted for covariates, first based on all children and then based on full siblings, using each of the 3 models. The results are summarized in Tables 7-19 through 7-21.

Table 7-19

P-Value Summary of Unadjusted Pre-post Initial Dioxin (Model 1)
 Analysis of Two-Category Severity
 (Major, Not Major)

Sibship	p-Value	
	D>10 ppt	D>5 ppt
All Children	NS	NS
Full Siblings	NS	NS

Table 7-20

P-Value Summary of Pre-post Current Dioxin (Model 2)
 and Time Analyses of Two-Category Severity
 (Major, Not Major)

Sibship	p-Value	
	D>10 ppt	D>5 ppt
All Children	NS	NS
Full Siblings	NS	NS

Table 7-21

P-Value Summary of Pre-post Categorized Current Dioxin (Model 3)
 Analyses of Two-Category Severity
 (Major, Not Major)

Sibship	All	Unadjusted Contrasts with Background		
		Unknown	Low	High
All Children	NS	NS	0.038	NS
Full Siblings	NS	NS	0.030	NS

Pre-post SEA analyses of birth defect severity in two categories (major, not major) found significant associations in Model 3 but not in Model 1 or Model 2 analyses. The Model 3 findings are caused by the rate of major post-SEA defects being elevated in Ranch Hands in the Low current dioxin category relative to Comparisons in the Background category. In the analysis of all children, the Low and Background post-SEA rates were 126.4 per 1000 and 57.1 per 1000; in full sibling children the rates were 121.6 per 1000 and 56.7 per 1000. However, the rate of major defects was not significantly elevated in children of Ranch Hands in the High dioxin category. The post-SEA rate in all children of Ranch Hands in the High category was 57.3 per 1000 and the rate in full sibling children of Ranch Hands in this category was 46.2 per 1000. We conclude that there is no consistent evidence that post-SEA birth defect severity is associated with dioxin after adjustment for pre-SEA severity.

Assessments of the association between the father's dioxin level and post-SEA birth defect severity in 3 categories (major, minor, none) were carried out using Models 1, 2 and 3 without adjustment for covariates. Each series of analyses was applied first to all children and then to full siblings. Assessments of the association between the father's dioxin level and post-SEA birth defect severity in 2 categories (major, not major) were carried out using Models 1, 2 and 3 without and then with adjustment for covariates. Each series of analyses was applied first to all children and then to full siblings. The results are summarized in Tables 7-22 through 7-24.

Table 7-22

P-Value Summary of Initial Dioxin Analyses of (Model 3)
Post-SEA Birth Defect Severity

Variable	Unadjusted		Adjusted	
	D>10 ppt	D>5 ppt	D>10 ppt	D>5 ppt
Severity (3 category)	NS	NS	--	--
Severity (2 category)	NS	NS	NS	NS

Table 7-22 (Continued)

b) Full Siblings

Variable	Unadjusted		Adjusted	
	D>10 ppt	D>5 ppt	D>10 ppt	D>5 ppt
Severity (3 category)	NS	NS	--	--
Severity (2 category)	NS	NS	NS	NS

Table 7-23

P-Value Summary of Current Dioxin and Time Analyses (Model 2) of Post-SEA Birth Defect Severity

a) All Children

Variable	Unadjusted					
	D>10 ppt			D>5 ppt		
	Dioxin by Time	Time Since SEA (years) ≤18.6	Time Since SEA (years) >18.6	Dioxin by Time	Time Since SEA (years) ≤18.6	Time Since SEA (years) >18.6
Severity (3 category)	NS	NS	NS	NS	NS	0.032
Severity (2 category)	NS	NS	NS	NS	NS	NS

b) All Children

Variable	Adjusted					
	D>10 ppt			D>5 ppt		
	Dioxin by Time	Time Since SEA (years) ≤18.6	Time Since SEA (years) >18.6	Dioxin by Time	Time Since SEA (years) ≤18.6	Time Since SEA (years) >18.6
Severity (3 category)	--	--	--	--	--	--
Severity (2 category)	**NS	**NS	**NS	NS	NS	NS

Table 7-23 (Continued)

c) Full Siblings

Variable	Unadjusted					
	Dioxin by Time	D>10 ppt Time Since SEA (years)		Dioxin by Time	D>5 ppt Time Since SEA (years)	
		≤18.6	>18.6		≤18.6	>18.6
Severity (3 category)	NS	NS	NS	NS	NS	0.016
Severity (2 category)	NS	NS	NS	NS	NS	NS

d) Full Siblings

Variable	Adjusted					
	Dioxin by Time	D>10 ppt Time Since SEA (years)		Dioxin by Time	D>5 ppt Time Since SEA (years)	
		≤18.6	>18.6		≤18.6	>18.6
Severity (3 category)	--	--	--	--	--	--
Severity (2 category)	NS	NS	NS	NS	NS	NS

Table 7-24

P-Value Summary of Categorized Current Dioxin Analyses of Post-SEA Birth Defect Severity (Model 3)

a) All Children

Variable	Unadjusted			
	All	Contrasts with Background		
		Unknown	Low	High
Severity (3 category)	0.033	NS	0.002	NS
Severity (2 category)	0.018	NS	0.001	NS

b) All Children

Variable	Adjusted			
	All	Contrasts with Background		
		Unknown	Low	High
Severity (3 category)	--	--	--	--
Severity (2 category)	****	****	****	****

Table 7-24 (Continued)

c) Full Siblings

Variable	All	Unadjusted		
		Contrasts with Background		
		Unknown	Low	High
Severity (3 category)	0.028	NS	0.010	NS
Severity (2 category)	0.033	NS	0.005	NS

d) Full Siblings

Variable	All	Adjusted		
		Contrasts with Background		
		Unknown	Low	High
Severity (3 category)	--	--	--	--
Severity (2 category)	NS*	NS	0.014	NS

Model 2 analyses of severity in 3 categories found significant associations with dioxin in all children and in full siblings, but Tables 7-9 and 7-15 show that these findings were caused by the highest rate of major defect occurring in children of Ranch Hands having intermediate dioxin levels. Corresponding analyses of severity in 2 categories were negative. These findings are not suggestive of a dioxin effect.

Without and with restriction to full sibling children, unadjusted Model 3 analyses of severity in 3 and in 2 categories found significant differences between children of Ranch Hands in the Low dioxin category and children of Comparisons in the Background dioxin category. Tables 7-11, 7-12, 7-17 and 7-18 show, however, that these findings are caused by a high rate of major defects in children of fathers in the Low dioxin category relative to children of fathers in the Background category, while the rate of major defects in children of fathers in the High dioxin category is not significantly elevated. These patterns are consistent with those of the Model 2 analyses but are not suggestive of a dioxin effect.

An adjusted Model 3 analysis of severity in 2 categories found significant interactions with the mother's smoking and the father's military occupation in SEA. However, within 4 of the 6 smoking by occupation strata the children of fathers in the High dioxin category had the lowest rate of major defects. The two significant findings in these strata were caused by the rate of major defects in children of Ranch Hands in the Low and Unknown dioxin categories being greater than that of children of Comparisons in the Background category.

In summary, analyses of birth defect severity found few significant associations. Those associations that were significant were generally caused by children of Ranch Hands with intermediate dioxin levels having the highest rates of major birth defects. In most of these analyses, children of Ranch Hands with the highest dioxin levels had the lowest rates of major defects. These patterns are inconsistent with the expected dose-response pattern and are not suggestive of a dioxin effect. We conclude that there is no evidence in these data to suggest that dioxin is associated with major birth defects.