

## 9. MULTIPLE BIRTH DEFECTS

### 9.1 Introduction

Of 1772 post-SEA live births, 66 were found to have multiple verified birth defects. The underlying physician narratives that determined the ICD coding of these birth defects were listed and examined for possible syndromes that could be attributed to dioxin. A listing of this data, together with a summary diagnosis for each is listed in Appendix Table G-1. Of these 66 children, 9 had defects consistent with recognized syndromes (Table 9-1). The child numbers in Table 9-1 correspond to those in Appendix Table G-1. Such syndromes (e.g. chromosomal anomalies and autosomal dominant mutations) could be theoretically associated with paternal dioxin exposures. The remaining 57 cases did not exhibit patterns of defects suggestive of any known syndromes. These 9 syndromic multiple defects are too few for analysis versus the father's dioxin level.

Table 9-1

#### Children with Genetic Syndromes

Child Number	Father's Group	Diagnosis and Site of Genetic Defect
1	Comparison	Down's Syndrome (chromosomal duplication)
4	Comparison	Down's Syndrome (chromosomal duplication)
13	Comparison	Achondroplasia (genetic-autosomal dominant)
23	Comparison	Treacher-Collins' Syndrome (autosomal dominant)
33	Ranch Hand	Down's Syndrome (chromosomal duplication)
53	Ranch Hand	Vater Syndrome
55	Ranch Hand	Down's Syndrome (chromosomal duplication)
57	Comparison	Down's Syndrome (chromosomal duplication)
62	Comparison	Sturge-Weber Syndrome

### 9.2 Post-SEA Exposure Analyses

Because there were so few children with multiple defects that could be attributed to known syndromes, the occurrence of "unexplained" multiple defects (those that could not be attributed to a known syndrome) were studied using Models 1, 2 and 3. In these analyses, post-SEA multiple defects that could not be related to a known syndrome were assessed versus paternal dioxin level without and with restriction to full siblings. The results are summarized in Tables 9-2 through 9-7.

**Multiple Defects (all Children)**

**Model 1: Children of Ranch Hands - Log<sub>2</sub>(Initial Dioxin)**

Without adjustment for covariates (Table 9-2 [a] and [b]), there is no significant association between multiple defects and initial dioxin among children of Ranch Hands having more than 10 ppt (p=0.445) or more than 5 ppt (p=0.402) current dioxin.

After adjustment for covariates (Table 9-2 [c] and [d]), there is no significant association between multiple defects and initial dioxin among children of Ranch Hands having more than 10 ppt (p=0.633) or more than 5 ppt (p=0.292) current dioxin.

**Table 9-2**

**Post-SEA Multiple Birth Defects**

Variable: Multiple Birth Defects  
 Restrictions: All Children of Ranch Hands  
 Children Conceived during or after the  
 Father's Duty in SEA  
 Model 1: Log<sub>2</sub>(Initial Dioxin)

<b>Ranch Hands - Log<sub>2</sub>(Initial) - Unadjusted</b>						
Exposure Restriction	Initial Dioxin	n	Anomaly Number	Anomaly Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=507)	Low	105	1	9.5	0.86(0.59,1.26)	0.445
	Medium	245	17	69.4		
	High	157	4	25.5		
b) D>5 ppt (n=688)	Low	154	1	6.5	1.13(0.85,1.49)	0.402
	Medium	307	15	48.9		
	High	227	8	35.2		

  

<b>Ranch Hands - Log<sub>2</sub>(Initial) - Adjusted</b>			
Exposure Restriction	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=415)	0.91(0.60,1.36)	0.633	None
d) D>5 ppt (n=563)	1.18(0.87,1.61)	0.292	None

## Multiple Defects (All Children)

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

Without adjustment for covariates (Table 9-3 [a]), there is no significant variation in the association between multiple defects and current dioxin with time since duty in SEA among children of Ranch Hands having more than 10 ppt current dioxin ( $p=0.267$ ). Furthermore, there is no significant association between multiple defects and current dioxin in children of Ranch Hands with late ( $p=0.824$ ) or early ( $p=0.159$ ) tours.

Without adjustment for covariates (Table 9-3 [b]), there is no significant variation in the association between multiple defects and current dioxin with time since duty in SEA among children of Ranch Hands having more than 5 ppt current dioxin ( $p=0.299$ ). Furthermore, there is no significant association between multiple defects and current dioxin in children of Ranch Hands with late ( $p=0.208$ ) or early ( $p=0.911$ ) tours.

After adjustment for covariates (Table 9-3 [c]), there is no significant variation in the association between multiple defects and current dioxin with time since duty in SEA among children of Ranch Hands having more than 10 ppt current dioxin ( $p=0.214$ ). Furthermore, there is no significant association between multiple defects and current dioxin in children of Ranch Hands with late ( $p=0.595$ ) or early ( $p=0.164$ ) tours.

After adjustment for covariates (Table 9-3 [d]), there is no significant variation in the association between multiple defects and current dioxin with time since duty in SEA among children of Ranch Hands having more than 5 ppt current dioxin ( $p=0.428$ ). Furthermore, there is no significant association between multiple defects and current dioxin in children of Ranch Hands with late ( $p=0.280$ ) or early ( $p=0.872$ ) tours.

Table 9-3

Post-SEA Multiple Birth Defects

Variable: Multiple Birth Defects  
 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)	Anomaly (No./n) Current Dioxin			Est. Relative Risk (95% C.I.)	p-Value
		Low	Medium	High		
a) D>10 ppt (n=508)						0.267
	≤18.6	16.1 (1/62)	52.2 (7/134)	27.8 (2/72)	1.07(0.59,1.94)	0.824
	>18.6	25.6 (1/39)	83.3 (9/108)	21.5 (2/93)	0.68(0.40,1.16)	0.159
b) D>5 ppt (n=688)						0.299
	≤18.6	0.0 (0/89)	40.2 (7/174)	36.4 (4/110)	1.33(0.85,2.09)	0.208
	>18.6	0.0 (0/63)	74.1 (10/135)	25.6 (3/117)	0.98(0.67,1.43)	0.911
Ranch Hands - $\text{Log}_2(\text{Current Dioxin}), \text{Time}$ - Adjusted						
Exposure Restriction	Time Since SEA (years)	Adj. Relative Risk (95% C.I.)		p-Value	Covariate Remarks	
c) D>10 ppt (n=416)				0.214	None	
	≤18.6	1.22(0.58,2.55)		0.595		
	>18.6	0.68(0.40,1.17)		0.164		
d) D>5 ppt (n=563)				0.428	None	
	≤18.6	1.35(0.78,2.34)		0.280		
	>18.6	1.03(0.70,1.52)		0.872		

## Multiple Defects (All Children)

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

Without adjustment for covariates (Table 9-4 [a]), there is a significant overall association between multiple defects and categorized dioxin ( $p=0.046$ ). The rate of multiple defects (69.0 per 1000) in children of Ranch Hands in the Low category is significantly greater than that of children of Comparisons in the Background category (30.8 per 1000);  $p=0.016$ . There is no significant difference between the rates in children of Ranch Hands in the High ( $p=0.996$ ) and Unknown ( $p=0.254$ ) categories with that of children of Comparisons in the background category.

After adjustment for covariates (Table 9-4 [b]), there is a significant overall association between multiple defects and categorized dioxin ( $p=0.041$ ). The rate of multiple defects in children of Ranch Hands in the Low category is significantly greater than that of children of Comparisons in the Background category ( $p=0.043$ ). There is no significant difference between the rate in children of Ranch Hands in the High ( $p=0.880$ ) and Unknown ( $p=0.121$ ) categories with that of children of Comparisons in the Background category.

Table 9-4

#### Post-SEA Multiple Birth Defects

Variable: Multiple Birth Defects  
 Restrictions: All Children of Ranch Hands  
 Children Conceived during or after the  
 Father's Duty in SEA  
 Model 3: Categorized Current Dioxin

#### a) Unadjusted

Exposure Category	n	Anomaly Number	Anomaly Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	975	30	30.8	All Exp Categ		0.046
Unknown	280	5	17.9	Unk vs Bkgd	0.57(0.22,1.49)	0.254
Low	174	12	69.0	Low vs Bkgd	2.43(1.17,4.65)	0.016
High	227	7	30.8	High vs Bkgd	1.00(0.43,2.31)	0.996
Total	1656					

Table 9-4 (Continued)

b) Adjusted

Exposure Category	n	Category Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	782	All Exp Categ		0.041	None
Unknown	228	Unk vs Bkgd	0.39(0.12,1.29)	0.121	
Low	144	Low vs Bkgd	2.17(1.02,4.61)	0.043	
High	193	High vs Bkgd	0.93(0.38,2.30)	0.880	
Total	1347				

Multiple Defects (Full Siblings)

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

Without adjustment for covariates (Table 9-5 [a] and [b]), there is no significant association between multiple defects and initial dioxin among full sibling children of Ranch Hands having more than 10 ppt ( $p=0.370$ ) or more than 5 ppt ( $p=0.605$ ) current dioxin.

After adjustment for covariates (Table 9-5 [c] and [d]), there is no significant association between multiple defects and initial dioxin among full sibling children of Ranch Hands having more than 10 ppt ( $p=0.565$ ) or more than 5 ppt ( $p=0.475$ ) current dioxin.

Table 9-5

Post-SEA Multiple Birth Defects

Variable: Multiple Birth Defects  
 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 - $\text{Log}_2(\text{Initial})$ - Unadjusted						
Exposure Restriction	Initial Dioxin	n	Anomaly Number	Anomaly Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=420)	Low	78	1	12.8	0.82(0.53,1.27)	0.370
	Medium	206	13	63.1		
	High	136	3	22.1		
b) D>5 ppt (n=556)	Low	113	1	8.8	1.09(0.79,1.51)	0.605
	Medium	245	10	40.8		
	High	198	7	35.4		
Ranch Hands - $\text{Log}_2(\text{Initial})$ - Adjusted						
Exposure Restriction	Adj. Relative Risk (95% C.I.)		p-Value		Covariate Remarks	
c) D>10 ppt (n=364)	0.88(0.56,1.38)		0.565		None	
d) D>5 ppt (n=612)	1.13(0.81,1.59)		0.475		None	

Multiple Defects (Full Siblings)

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

Without adjustment for covariates (Table 9-6 [a]), there is no significant variation in the association between multiple defects and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 10 ppt current dioxin ( $p=0.290$ ). Furthermore, there is no significant association between multiple defects and current dioxin in children of Ranch Hands with late ( $p=0.995$ ) or early ( $p=0.137$ ) tours.

Without adjustment for covariates (Table 9-6 [b]), there is no significant variation in the association between multiple defects and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 5 ppt current dioxin ( $p=0.543$ ). Furthermore, there is no significant association between multiple defects and current dioxin in children of Ranch Hands with late ( $p=0.452$ ) or early ( $p=0.943$ ) tours.

After adjustment for covariates (Table 9-6 [c]), there is no significant variation in the association between multiple defects and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 10 ppt current dioxin ( $p=0.174$ ). Furthermore, there is no significant association between multiple defects and current dioxin in children of Ranch Hands with late ( $p=0.619$ ) or early ( $p=0.138$ ) tours.

After adjustment for covariates (Table 9-6 [d]), there is no significant variation in the association between multiple defects and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 5 ppt current dioxin ( $p=0.435$ ). Furthermore, there is no significant association between multiple defects and current dioxin in children of Ranch Hands with late ( $p=0.346$ ) or early ( $p=0.948$ ) tours.

Table 9-6

Post-SEA Multiple Birth Defects

Variable: Multiple Birth Defects  
 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)	Anomaly (No./n) Current Dioxin			Est. Relative Risk (95% C.I.)	p-Value
		Low	Medium	High		
a) D>10 ppt (n=421)						0.290
	≤18.6	21.3 (1/47)	43.5 (5/115)	31.3 (2/64)	1.00(0.51,1.96)	0.995
	>18.6	35.7 (1/28)	76.1 (7/92)	13.3 (1/75)	0.60(0.31,1.17)	0.137
b) D>5 ppt (n=556)						0.543
	≤18.6	0.0 (0/58)	41.7 (6/144)	30.6 (3/98)	1.21(0.73,2.01)	0.452
	>18.6	0.0 (0/53)	66.0 (7/106)	20.6 (2/97)	0.98(0.63,1.54)	0.943
Ranch Hands - $\text{Log}_2(\text{Current Dioxin}), \text{Time}$ - Adjusted						
Exposure Restriction	Time Since SEA (years)	Adj. Relative Risk (95% C.I.)		p-Value	Covariate Remarks	
c) D>10 ppt (n=365)				0.174	None	
	≤18.6	1.21(0.57,2.54)		0.619		
	>18.6	0.61(0.32,1.17)		0.138		
d) D>5 ppt (n=486)				0.435	None	
	≤18.6	1.31(0.75,2.28)		0.346		
	>18.6	0.99(0.63,1.53)		0.948		

**Multiple Defects (Full Siblings)**

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

Without adjustment for covariates (Table 9-7 [a]), there is a borderline significant overall association between multiple defects and categorized dioxin among full siblings ( $p=0.087$ ). The rate of multiple defects (67.6 per 1000) in children of Ranch Hands in the Low category is significantly greater than that of children of Comparisons in the Background category (29.8 per 1000);  $p=0.026$ . There is no significant difference between the rate in children of Ranch Hands in the High ( $p=0.757$ ) and Unknown ( $p=0.359$ ) categories with that of children of Comparisons in the Background category.

After adjustment for covariates (Table 9-7 [b]), there is a borderline significant overall association between multiple defects and categorized dioxin among full siblings ( $p=0.090$ ). The rate of multiple defects in children of Ranch Hands in the Low category is significantly greater than that in children of Comparisons in the Background category ( $p=0.051$ ). There is no significant difference between the rates in children of Ranch Hands in the High ( $p=0.735$ ) and Unknown ( $p=0.238$ ) categories with that of children of Comparisons in the Background category.

**Table 9-7**

**Post-SEA Multiple Birth Defects**

Variable: Multiple Birth Defects  
 Restrictions: Full Siblings of Ranch Hands  
 Children Conceived during or after the  
 Father's Duty in SEA  
 Model 3: Categorized Current Dioxin

**a) Unadjusted**

Exposure Category	n	Anomaly Number	Anomaly Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	806	24	29.8	All Exp Categ		0.087
Unknown	219	4	18.3	Unk vs Bkgd	0.61(0.21,1.77)	0.359
Low	148	10	67.6	Low vs Bkgd	2.36(1.10,5.05)	0.026
High	195	5	25.6	High vs Bkgd	0.86(0.32,2.28)	0.757
Total	1368					

Table 9-7 (Continued)

b) Adjusted

Exposure Category	n	Category Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	667	All Exp Categ		0.090	DRINK(p=0.017)
Unknown	190	Unk vs Bkgd	0.48(0.14,1.63)	0.238	
Low	127	Low vs Bkgd	2.23(1.00,5.021)	0.051	
High	174	High vs Bkgd	0.84(0.31,2.27)	0.735	
Total	1158				

9.3 Conclusion

Multiple birth defects were defined as more than one birth defect in a pattern that could not be attributed to a recognized syndrome. The association between multiple birth defects and dioxin was investigated with Models 1, 2 and 3 in post-SEA children without and with restriction to full siblings. The results are summarized in Tables 9-8 through 9-10.

Table 9-8

P-Value Summary of Initial Dioxin (Model 1)  
Analyses of Post-SEA Multiple Birth Defects

Sibship	Unadjusted		Adjusted	
	D>10 ppt	D>5 ppt	D>10 ppt	D>5 ppt
All Children	NS	NS	NS	NS
Full Siblings	NS	NS	NS	NS

Table 9-9

P-Value summary of Current Dioxin and Time (Model 2)  
Analyses of Multiple Defects

a) Unadjusted

Sibship	Dioxin by Time	Time Since SEA (years)	
		≤18.6	>18.6
All Children	NS	NS	NS
Full Siblings	NS	NS	NS

b) Adjusted

Sibship	Dioxin by Time	Time Since SEA (years)	
		≤18.6	>18.6
All Children	NS	NS	NS
Full Siblings	NS	NS	NS

Table 9-10

P-Value Summary of Categorized Current Dioxin (Model 3)  
Analyses of Multiple Defects

a) Unadjusted

Sibship	All	Contrasts with Background		
		Unknown	Low	High
All Children	0.046	NS	0.016	NS
Full Siblings	NS*	NS	0.026	NS

b) Adjusted

Sibship	All	Contrasts with Background		
		Unknown	Low	High
All Children	0.041	NS	0.043	NS
Full Siblings	NS*	NS	0.051	NS

Model 1 and 2 analyses of multiple defects found no significant associations. Model 3 analyses found significantly increased rates of multiple defects in children of Ranch Hands in the Low dioxin category relative to the rate in children of Comparisons in the Background category. However, the rate in children of Ranch Hands in the High dioxin category were not significantly increased relative to background. These results inconsistent with the expected dose response and are most likely not related to dioxin.

In summary, there is no evidence in these data that dioxin is adversely associated with multiple birth defects.