Table 8-16

Post-SEA Counts and Rates of Specific Delays in Development

Variable: Specific Delays in Development
Restrictions: All Children of Ranch Hands
Children Conceived during or after the Father's Duty in SEA
Model 1: Log_2(Initial Dioxin)

Ranch Hands - Log_2(Initial Dioxin) - Unadjusted

Exposure Restriction	Initial Dioxin	n	Anomaly Number	Anomaly Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=508)	Low	106	12	113.2	0.88(0.67,1.14)	0.321
	Medium	245	25	102.0		
	High	157	10	63.7		
b) D>5 ppt (n=690)	Low	155	13	83.9	0.97(0.80,1.17)	0.758
	Medium	308	29	94.2		
	High	227	18	79.3		

Ranch Hands - Log_2(Initial Dioxin) - Adjusted

Exposure Restriction	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=458)	0.88(0.68,1.14)	0.318	C-TIME(p=0.061)
d) D>5 ppt (n=616)	0.99(0.82,1.20)	0.900	C-TIME(p=0.005)

Specific Delays in Development (All Children)

Model 2: Children of Ranch Hands - Log_2(Current Dioxin) and Time

Without adjustment for covariates (Table 8-17 [a]), there is no significant variation in the association between specific delays in development and current dioxin with time since duty in SEA among children of Ranch Hands having more than 10 ppt current dioxin (p=0.937). Furthermore, there is no significant association between specific delays in development and current dioxin in children whose fathers had late (p=0.429) or early (p=0.431) tours.

Without adjustment for covariates (Table 8-17 [b]), there is no significant variation in the association between specific delays in development and current dioxin with time since duty in SEA in children of Ranch Hands having more than 5 ppt current dioxin (p=0.538). Furthermore, there is no significant association between specific delays in development and current dioxin in children whose fathers had early (p=0.624) or late (p=0.706) tours.

After adjustment for covariates (Table 8-17 [c]), there is no significant variation in the association between specific delays in development and current dioxin with time since duty in SEA among children of Ranch Hands having more than 10 ppt current dioxin (p=0.812). Furthermore, there is no significant association between specific delays in development and current dioxin in children whose fathers had late (p=0.581) or early (p=0.376) tours.

After adjustment for covariates (Table 8-17 [d]), there is no significant variation in the association between specific delays in development and current dioxin with time since duty in SEA among children of Ranch Hands having more than 5 ppt current dioxin (p=0.468). Furthermore, there is no significant association between specific delays in development and current dioxin in children whose fathers had late (p=0.616) or early (p=0.601) tours.

Table 8-17

Post-SEA Counts and Rates of Specific Delays in Development

Variable: Specific Delays in Development
Restrictions: All Children of Ranch Hands
Children Conceived during or after the Father's Duty in SEA
Model 2: Log_2(Current Dioxin), Time

Ranch Hands - Log_2(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time Since SEA (years)	Current Dioxin Anomaly Rate (No./n) Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=509)						0.937
	≤18.6	96.8 (6/62)	104.5 (14/134)	55.6 (4/72)	0.84(0.56,1.28)	0.429
	>18.6	100.0 (4/40)	111.1 (12/108)	75.3 (7/93)	0.86(0.60,1.24)	0.431
b) D>5 ppt (n=690)						0.538
	≤18.6	88.9 (8/90)	103.4 (18/174)	72.7 (8/110)	0.93(0.70,1.23)	0.624
	>18.6	47.6 (3/63)	110.3 (15/136)	68.4 (8/117)	1.05(0.80,1.38)	0.706

Table 8-17 (Continued)

Ranch Hands - Log_2(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)			0.812	C-TIME(p=0.059)
	≤18.6	0.78(0.31,1.92)	0.581	
	>18.6	0.83(0.55,1.25)	0.376	
d) D>5 ppt (n=616)			0.468	C-TIME(p=0.005)
	≤18.6	0.93(0.70,1.23)	0.616	
	>18.6	1.08(0.82,1.41)	0.601	

Specific Delays in Development (All Children)

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

Without adjustment for covariates (Table 8-18 [a]), there is no significant overall association between specific delays in development and categorized current dioxin (p=0.293). However, the rate of specific delays in development among children of Ranch Hands in the Low category, 114.9 per 1000, is borderline significantly greater than the rate among children of Comparisons in the Background category ,72.4 per 1000 (p=0.057). The rates of specific delays in development among children of Ranch Hands in the High category (p=0.921) and among children of Ranch Hands in the Unknown category (p=0.475) are not significantly different from the rate in children of Comparisons in the Background category.

After adjustment for covariates (Table 8-18 [b]), there is no significant overall association between specific delays in development and categorized current dioxin (p=0.142). However, the rate of specific delays in development among children of Ranch Hands in the Low category, is significantly greater than the rate among children of Comparisons in the Background category (p=0.042). There is no significant difference between the rates of specific delays in development among children of Ranch Hands in the High category (p=0.682) or among children of Ranch Hands in the Unknown category (p=0.226) with the rate in children of Comparisons in the Background category.

Table 8-18

Post-SEA Counts and Rates of Specific Delays in Development

Variable: Specific Delays in Development
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	Anomaly Number	Anomaly Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	981	71	72.4	All Exp Categ		0.293
Unknown	282	24	85.1	Unk vs Bkgd	1.19(0.74,1.93)	0.475
Low	174	20	114.9	Low vs Bkgd	1.66(0.98,2.81)	0.057
High	227	16	70.5	High vs Bkgd	0.97(0.55,1.71)	0.921
Total	1664					

b) Adjusted

Exposure Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	843	All Exp Categ		0.142	RACE(p=0.017)
Unknown	246	Unk vs Bkgd	1.37(0.82,2.28)	0.226	OCC(p=0.005)
Low	156	Low vs Bkgd	1.76(1.02,3.04)	0.042	SMOKE(p=0.031)
High	203	High vs Bkgd	0.88(0.49,1.59)	0.682	C-TIME(p=0.004)
Total	1448				

Specific Delays in Development (Full Siblings)

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

Without adjustment for covariates (Table 8-19 [a] and [b]), there is no significant association between specific delays in development and initial dioxin among full sibling children of Ranch Hands with more than 10 ppt (p=0.468) or more than 5 ppt (p=0.919) current dioxin.

After adjustment for covariates (Table 8-19 [c]), there is no significant association between specific delays in development and initial dioxin among full sibling children of Ranch Hands with more than 10 ppt current dioxin (p=0.190) or with more than 5 ppt current dioxin (p=0.982).

Table 8-19

Post-SEA Counts and Rates of Specific Delays in Development

Variable: Specific Delays in Development
Restrictions: Full Siblings of Ranch Hands
Children Conceived during or after the Father's Duty in SEA
Model 1: Log_2(Initial Dioxin)

Ranch Hands - Log_2(Initial Dioxin) - Unadjusted

Exposure Restriction	Initial Dioxin	n	Anomaly Count	Anomaly Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=420)	Low	78	10	128.2	0.90(0.68,1.19)	0.468
	Medium	206	21	101.9		
	High	136	10	73.5		
b) D>5 ppt (n=557)	Low	114	10	87.7	0.99(0.81,1.21)	0.919
	Medium	245	23	93.9		
	High	198	18	90.9		

Ranch Hands - Log_2(Initial Dioxin) - Adjusted

Exposure Restriction	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=390)	0.82(0.60,1.11)	0.190	C-TIME(p=0.003) F-AGE(p=0.018) OCC(p=0.039)
d) D>5 ppt (n=513)	1.00(0.82,1.23)	0.982	C-TIME(p=(0.015)

Specific Delays in Development (Full Siblings)

Model 2: Children of Ranch Hands - Log_2(Current Dioxin) and Time

Without adjustment for covariates (Table 8-20 [a]), there is no significant variation in the association between specific delays in development and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 10 ppt current dioxin (p=0.704). Furthermore, there is no significant association between specific delays in development and current dioxin in children of fathers who had late (p=0.471) or early (p=0.815) tours.

Without adjustment for covariates (Table 8-20 [b]), there is no significant variation in the association between specific delays in development and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 5 ppt current dioxin (p=0.530). Furthermore, there is no significant association between specific delays in development and current dioxin in children of fathers who had late (p=0.759) or early (p=0.557) tours.

After adjustment for covariates (Table 8-20 [c]), there is no significant variation in the association between specific delays in development and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 10 ppt current dioxin (p=0.857). Furthermore, there is no significant association between specific delays in development and current dioxin in children of fathers who had late (p=0.541) or early (p=0.285) tours.

After adjustment for covariates (Table 8-20 [d]), there is no significant variation in the association between specific delays in development and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 5 ppt current dioxin (p=0.522). Furthermore, there is no significant association between specific delays in development and current dioxin in children of fathers who had late (p=0.591) or early (p=0.761) tours.

Table 8-20

Post-SEA Counts and Rates of Specific Delays in Development

Variable: Specific Delays in Development
Restrictions: Full Siblings of Ranch Hands
Children Conceived during or after the Father's Duty in SEA
Model 2: Log_2(Current Dioxin), Time

Ranch Hands - Log_2(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time Since SEA (years)	Current Dioxin Anomaly Rate (No./n) Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=421)						0.704
	≤18.6	106.4 (5/47)	113.0 (13/115)	62.5 (4/64)	0.85(0.55,1.32)	0.471
	>18.6	107.1 (3/28)	97.8 (9/92)	93.3 (7/75)	0.95(0.65,1.41)	0.815
b) D>5 ppt (n=557)						0.530
	≤18.6	84.7 (5/59)	111.1 (16/144)	81.6 (8/98)	0.95(0.70,1.29)	0.759
	>18.6	56.6 (3/53)	103.8 (11/106)	82.5 (8/97)	1.09(0.82,1.46)	0.557

Table 8-20 (Continued)

Ranch Hands - Log_2(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)			0.857	C-TIME(p=0.003) OCC(p=0.032)
	≤18.6	0.73(0.26,2.01)	0.541	F-AGE(p=0.026)
	>18.6	0.77(0.48,1.24)	0.285	
d) D>5 ppt (n=513)			0.522	C-TIME(p=0.014)
	≤18.6	0.83(0.42,1.64)	0.591	
	>18.6	0.95(0.70,1.29)	0.761	

Specific Delays in Development (Full Siblings)

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

Without adjustment for covariates (Table 8-21 [a]), there is no significant overall association between specific delays in development and categorized current dioxin among full siblings (p=0.550). Furthermore, there is no significant difference between the rate of specific delays in development in children of Ranch Hands in the High (p=0.835), Low (p=0.134) or Unknown (p=0.850) categories and the rate in children of Comparisons in the Background category.

After adjustment for covariates (Table 8-21 [b]), there is no significant variation in the overall association between specific delays in development and categorized current dioxin with the father's age at the time of conception (p=0.006) and the time of conception (p=0.005). The basis for this variation is displayed in Appendix Table F-1. There is a significantly elevated risk in children of Ranch Hands in the Low category (OR=6.48, 95% CI 1.78-23.5, p=0.004) conceived within 4 years of duty in SEA whose father was more than 30 years old at the time of conception. In the same stratum, the contrast of children of Ranch Hands in the High category with children of Comparisons in the Background category was of borderline significance (p=0.099), as was the contrast of children of Ranch Hands in the Unknown category with children of Comparisons in the Background category (p=0.075). The contrasts with the Background category are not significant in the remaining strata.

Table 8-21

Post-SEA Counts and Rates of Specific Delays in Development

Variable: Specific Delays in Development
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**

Exposure Category	n	Anomaly Count	Anomaly Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	812	63	77.6	All Exp Categ		0.550
Unknown	221	18	81.4	Unk vs Bkgd	1.05(0.61,1.82)	0.850
Low	148	17	114.9	Low vs Bkgd	1.54(0.88,2.72)	0.134
High	195	16	82.1	High vs Bkgd	1.06(0.60,1.88)	0.835
Total	1376					

b) **Adjusted**

Exposure Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	715	All Exp Categ		****	RACE(p=0.004)
Unknown	199	Unk vs Bkgd	****	****	SMOKE(p=0.002)
Low	137	Low vs Bkgd	****	****	DIOXIN*F-AGE
High	180	High vs Bkgd	****	****	(p=0.006)
Total	1231				DIOXIN*C-TIME (p=0.005)

Hyperkinetic Syndrome of Childhood (All Children)

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

Without adjustment for covariates (Table 8-22 [a] and [b]), there is no significant association between hyperkinetic syndrome and initial dioxin among children of Ranch Hands having more than 10 ppt (p=0.939) or more than 5 ppt (p=0.277) current dioxin.

After adjustment for covariates (Table 8-22 [c] and [d]), there is no significant association between hyperkinetic syndrome and initial dioxin among children of Ranch Hands having more than 10 ppt (p=0.988) or more than 5 ppt (p=0.162) current dioxin.

Table 8-22

Post-SEA Counts and Rates of Hyperkinetic Syndrome of Childhood

Variable: Hyperkinetic Syndrome of Childhood
Restrictions: All Children of Ranch Hands
Children Conceived during or after the Father's Duty in SEA
Model 1: Log_2(Initial Dioxin)

Ranch Hands - Log_2(Initial Dioxin) - Unadjusted

Exposure Restriction	Initial Dioxin	n	Anomaly Count	Anomaly Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=508)	Low	106	3	28.3	1.02(0.67,1.55)	0.939
	Medium	245	7	28.6		
	High	157	6	38.2		
b) D>5 ppt (n=690)	Low	155	10	64.5	0.86(0.65,1.14)	0.277
	Medium	308	8	26.0		
	High	227	10	44.1		

Ranch Hands - Log_2(Initial Dioxin) - Adjusted

Exposure Restriction	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=458)	0.99(0.64,1.55)	0.988	RACE(p=0.094)
d) D>5 ppt (n=616)	0.81(0.60,1.10)	0.162	RACE(p=0.030)

Hyperkinetic Syndrome of Childhood (All Children)

Model 2: Children of Ranch Hands - Log_2(Current Dioxin) and Time

Without adjustment for covariates (Table 8-23 [a]), there is borderline significant variation in the association between hyperkinetic syndrome and current dioxin with time since duty in SEA among children of Ranch Hands with more than 10 ppt current dioxin (p=0.086). There is no significant association between hyperkinetic syndrome and dioxin in children of Ranch Hands who had late tours (p=0.142) and no significant risk among children of Ranch Hands who had early tours (p=0.359). The borderline significant interaction is caused by an increasing trend in children of fathers with late tours and a decreasing trend in children of fathers with early tours, but neither of these trends are significant.

Without adjustment for covariates (Table 8-23 [b]), there is no significant variation in the association between hyperkinetic syndrome and current dioxin with time since duty in SEA among children of Ranch Hands having more than 5 ppt current dioxin (p=0.139). There is no significant association between hyperkinetic syndrome and current dioxin in children of fathers who had late (p=0.679) tours. However, there is a borderline significant association between hyperkinetic syndrome and current dioxin in children of fathers who had early (p=0.101) tours; in that stratum, the rate of hyperkinetic syndrome decreases with dioxin.

After adjustment for covariates (Table 8-23 [c]), there is no significant variation in the association between hyperkinetic syndrome and current dioxin with time since duty in SEA among children of Ranch Hands having more than 10 ppt current dioxin (p=0.191). Furthermore, there is no significant association between hyperkinetic syndrome and current dioxin in children of fathers who had late (p=0.320) or early (p=0.402) tours.

After adjustment for covariates (Table 8-23 [d]), there is no significant variation in the association between hyperkinetic syndrome and current dioxin with time since duty in SEA among children of Ranch Hands having more than 5 ppt current dioxin (p=0.490). Furthermore, there is no significant association between hyperkinetic syndrome and current dioxin in children of fathers who had late (p=0.683) or early (p=0.154) tours.

Table 8-23

Post-SEA Counts and Rates of Hyperkinetic Syndrome of Childhood

Variable: Hyperkinetic Syndrome of Childhood
Restrictions: All Children of Ranch Hands
Children Conceived during or after the Father's Duty in SEA
Model 2: Log_2(Current Dioxin), Time

Ranch Hands - Log_2(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time Since SEA (years)	Current Dioxin Anomaly Rate (No./n) Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=509)						0.086
	≤18.6	0.0 (0/62)	29.9 (4/134)	55.6 (4/72)	1.61(0.85,3.04)	0.142
	>18.6	50.0 (2/40)	37.0 (4/108)	21.5 (2/93)	0.74(0.40,1.40)	0.359
b) D>5 ppt (n=690)						0.139
	≤18.6	33.3 (3/90)	28.7 (5/174)	54.5 (6/110)	1.09(0.72,1.64)	0.679
	>18.6	79.4 (5/63)	36.8 (5/136)	34.2 (4/117)	0.70(0.46,1.07)	0.101

Table 8-23 (Continued)

Ranch Hands - Log_2(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)			0.191	None
	≤18.6	1.44(0.70,2.96)	0.320	
	>18.6	0.77(0.42,1.42)	0.402	
d) D>5 ppt (n=616)			0.490	RACE(p=0.037)
	≤18.6	0.91(0.58,1.42)	0.683	
	>18.6	0.74(0.48,1.12)	0.154	

Hyperkinetic Syndrome of Childhood (All Children)

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

Without adjustment for covariates (Table 8-24 [a]), there is no significant overall association between hyperkinetic syndrome and categorized current dioxin (p=0.383). Furthermore, there is no significant difference between the rate of hyperkinetic syndrome in children of Ranch Hands in the High (p=0.399), Low (p=0.503) or Unknown (p=0.180) categories with the rate in children of Comparisons in the Background category.

After adjustment for covariates (Table 8-24) [b], there is no significant overall association between hyperkinetic syndrome and categorized current dioxin (p=0.618). Furthermore, there is no significant difference between the rates of hyperkinetic syndrome in children of Ranch Hands in the High (p=0.902), Low (p=0.539) or Unknown (p=0.289) categories and the rate in children of Comparisons in the Background category.

Table 8-24

Post-SEA Counts and Rates of Hyperkinetic Syndrome of Childhood

Variable: Hyperkinetic Syndrome of Childhood
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	Anomaly Count	Anomaly Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	981	32	32.6	All Exp Categ		0.383
Unknown	282	14	49.6	Unk vs Bkgd	1.55(0.81,2.95)	0.180
Low	174	4	23.0	Low vs Bkgd	0.70(0.24,2.00)	0.503
High	227	10	44.1	High vs Bkgd	1.37(0.66,2.82)	0.399
Total	1664					

b) **Adjusted**

Exposure Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	843	All Exp Categ		0.618	RACE(p=0.095)
Unknown	246	Unk vs Bkgd	1.43(0.74,2.79)	0.289	DRINK(p=0.045)
Low	156	Low vs Bkgd	0.72(0.25,2.07)	0.539	C-TIME(p=0.047)
High	203	High vs Bkgd	1.05(0.47,2.33)	0.902	
Total	1448				

Hyperkinetic Syndrome of Childhood (Full Siblings)

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

Without adjustment for covariates (Table 8-25 [a] and [b]), there is no significant association between hyperkinetic syndrome and initial dioxin among full sibling children of Ranch Hands having more than 10 ppt (p=0.892) and a borderline significant negative association between hyperkinetic syndrome and initial dioxin among full sibling children of Ranch Hands having more than 5 ppt (p=0.058) current dioxin.

After adjustment for covariates (Table 8-25 [c] and [d]), there is no significant association between hyperkinetic syndrome and initial dioxin among full sibling children of Ranch Hands having more than 10 ppt (p=0.880); however, there is a significant negative association between hyperkinetic syndrome and initial dioxin among full sibling children of Ranch Hands having more than 5 ppt (p=0.053).

Table 8-25

Post-SEA Counts and Rates of Hyperkinetic Syndrome of Childhood

Variable: Hyperkinetic Syndrome of Childhood
Restrictions: Full Siblings of Ranch Hands
Children Conceived during or after the Father's Duty in SEA
Model 1: Log_2(Initial Dioxin)

Ranch Hands - Log_2(Initial Dioxin) - Unadjusted

Exposure Restriction	Initial Dioxin	n	Anomaly Count	Anomaly Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=420)	Low	78	2	25.6	0.96(0.58,1.61)	0.892
	Medium	206	5	24.3		
	High	136	4	29.4		
b) D>5 ppt (n=557)	Low	114	10	87.7	0.73(0.52,1.03)	0.058
	Medium	245	5	20.4		
	High	198	7	35.4		

Ranch Hands - Log_2(Initial Dioxin) - Adjusted

Exposure Restriction	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=390)	0.96(0.58,1.60)	0.880	None
d) D>5 ppt (n=513)	0.73(0.52,1.02)	0.053	None

Hyperkinetic Syndrome of Childhood (Full Siblings)

Model 2: Children of Ranch Hands - Log_2(Current Dioxin) and Time

Without adjustment for covariates (Table 8-26 [a]), there is borderline significant variation in the association between hyperkinetic syndrome and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 10 ppt current dioxin (p=0.102). However, there is no significant association between hyperkinetic syndrome and current dioxin in children of fathers who had late (p=0.267) or early (p=0.231) tours. The borderline significant interaction was caused by an increasing trend in children of fathers with late tours and a decreasing trend in children of fathers with early tours, but neither of these trends were significant.

Without adjustment for covariates (Table 8-26 [b]), there is no significant variation in the association between hyperkinetic syndrome and current dioxin with time since duty in SEA of duty among full sibling children of Ranch Hands having more than 5 ppt current dioxin (p=0.594). There is no significant association between hyperkinetic syndrome and current dioxin in children of Ranch Hands who had late (p=0.410) tours; however, there is a borderline significant negative association between hyperkinetic syndrome and current dioxin in children of Ranch Hands who had early tours (p=0.082).

After adjustment for covariates (Table 8-26 [c]), there is no significant variation in the association between hyperkinetic syndrome and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 10 ppt current dioxin (p=0.114). Furthermore, there is no significant association between hyperkinetic syndrome and current dioxin in children of Ranch Hands who had late (p=0.285) or early (p=0.245) tours.

After adjustment for covariates (Table 8-26 [d]), there is no significant variation in the association between hyperkinetic syndrome and current dioxin with time since duty in SEA among full sibling children of Ranch Hands having more than 5 ppt current dioxin (p=0.631). There is no significant association between hyperkinetic syndrome and current dioxin in children of Ranch Hands who had late (p=0.372) tours, however, there is a borderline significant negative association between hyperkinetic syndrome and current dioxin in children of Ranch Hands who had early tours (p=0.082).

Table 8-26

Post-SEA Counts and Rates of Hyperkinetic Syndrome of Childhood

Variable: Hyperkinetic Syndrome of Childhood
Restrictions: Full Siblings of Ranch Hands
Children Conceived during or after the Father's Duty in SEA
Model 2: Log_2(Current Dioxin), Time

Ranch Hands - Log_2(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time Since SEA (years)	Current Dioxin Anomaly Rate (No./n) Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=421)						0.102
	≤18.6	0.0 (0/47)	17.4 (2/115)	31.3 (2/64)	1.65(0.68,4.02)	0.267
	>18.6	71.4 (2/28)	43.5 (4/92)	13.3 (1/75)	0.64(0.31,1.33)	0.231
b) D>5 ppt (n=557)						0.594
	≤18.6	50.8 (3/59)	27.8 (4/144)	30.6 (3/98)	0.80(0.47,1.36)	0.410
	>18.6	94.3 (5/53)	37.7 (4/106)	30.9 (3/97)	0.66(0.42,1.05)	0.082

Table 8-26 (Continued)

Ranch Hands - Log_2(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)			0.114	None
	≤18.6	1.62(0.67,3.92)	0.285	
	>18.6	0.66(0.32,1.33)	0.245	
d) D>5 ppt (n=513)			0.631	None
	≤18.6	0.79(0.46,1.33)	0.372	
	>18.6	0.66(0.42,1.05)	0.082	

Hyperkinetic Syndrome of Childhood (Full Siblings)

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

Without adjustment for covariates (Table 8-27 [a]), there is no significant overall association between hyperkinetic syndrome and categorized current dioxin among full sibling children (p=0.244). Furthermore, there is no significant difference between the rate of hyperkinetic syndrome among children of Ranch Hands in the High (p=0.735), Low (p=0.342) or Unknown (p=0.126) categories and the rate in children of Comparisons in the Background category.

After adjustment for covariates (Table 8-27 [b]), there is no significant overall association between hyperkinetic syndrome and categorized current dioxin among full sibling children (p=0.220). Furthermore, there is no significant difference between the rates of hyperkinetic syndrome among children of Ranch Hands in the High (p=0.715), Low (p=0.330) or Unknown (p=0.119) categories and the rate in children of Comparisons in the Background category.

Table 8-27

Post-SEA Counts and Rates of Hyperkinetic Syndrome of Childhood

Variable: Hyperkinetic Syndrome of Childhood
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**

Exposure Category	n	Anomaly Count	Anomaly Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	812	29	35.7	All Exp Categ		0.244
Unknown	221	13	58.8	Unk vs Bkgd	1.69(0.86,3.31)	0.126
Low	148	3	20.3	Low vs Bkgd	0.56(0.17,1.86)	0.342
High	195	6	30.8	High vs Bkgd	0.86(0.35,2.10)	0.735
Total	1376					

b) **Adjusted**

Exposure Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	715	All Exp Categ		0.220	DRINK(p=0.087)
Unknown	199	Unk vs Bkgd	1.71(0.87,3.38)	0.119	M-AGE(p=0.053)
Low	137	Low vs Bkgd	0.55(0.16,1.83)	0.330	C-TIME(p=0.051)
High	180	High vs Bkgd	0.85(0.34,2.08)	0.715	
Total	1231				

8.4 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.

Twelve selected birth defects: anencephaly, spina bifida, hydrocephalus, cleft palate, cleft lip/palate, esophageal atresia, anorectal atresia, polydactyly, limb reduction deformities, hypospacias, congenital hip dislocation, Down's syndrome, and 4 developmental disabilities: disturbance of emotion specific to childhood and adolescence, hyperkinetic syndrome of childhood, specific delays in development and mental retardation were considered for investigation. Of these, there were only enough occurrences of specific delays in development and hyperkinetic syndrome to permit assessment of associations with dioxin. There were too few occurrences in the other categories to permit any statistical analysis.

Assessments of the association between specific delays in development and hyperkinetic syndrome and dioxin were carried out based on all children (pre-SEA and post-SEA) using Models 1, 2 and 3. Each analysis was carried out without adjustment for covariates. All analyses were first based on all children and again full siblings. The results are summarized in Tables 8-28 through 8-30.

Table 8-28

P-Value Summary of Initial Dioxin (Model 1) Pre-Post SEA Analyses of Specific Delays in Development and Hyperkinetic Syndrome of Childhood (Children of Ranch Hands)

a) **All Children**

Anomaly	Unadjusted D>10 ppt	Unadjusted D>5 ppt
Specific Delays in Development	0.035	0.044
Hyperkinetic Syndrome of Childhood	NS	NS

b) **Full Siblings**

Anomaly	Unadjusted D>10 ppt	Unadjusted D>5 ppt
Specific Delays in Development	0.045	0.053
Hyperkinetic Syndrome of Childhood	NS	NS

Table 8-29

P-Value Summary of Current Dioxin and Time Pre-Post SEA Analyses (Model 2) of Specific Delays in Development and Hyperkinetic Syndrome of Childhood (Children of Ranch Hands)

a) All Children

Anomaly	Unadjusted D>10 ppt	Unadjusted D>5 ppt
Specific Delays in Development	NS*	0.032
Hyperkinetic Syndrome of Childhood	NS	NS

b) Full Siblings

Anomaly	Unadjusted D>10 ppt	Unadjusted D>5 ppt
Specific Delays in Development	NS*	NS*
Hyperkinetic Syndrome of Childhood	NS	NS

Table 8-30

P-Value Summary of Pre-Post-SEA Categorized Current Dioxin (Model 3) Analyses of Specific Delays in Development and Hyperkinetic Syndrome of Childhood (Children of Ranch Hands and Comparisons)

a) All Children

Anomaly	All	Unadjusted Contrasts with Background: Unknown	Low	High
Specific Delays in Development	NS	NS	NS	NS
Hyperkinetics Syndrome of Childhood	NS	NS	NS	NS*

b) Full Siblings

Anomaly	All	Unadjusted Contrasts with Background: Unknown	Low	High
Specific Delays in Development	NS	NS	NS	NS
Hyperkinetics Syndrome of Childhood	NS	NS	NS	NS

Assessment of the association between specific delays in development and hyperkinetic syndrome and dioxin were also carried out based on post-SEA children using Models 1 2 and 3. Each analysis was carried out without and then with adjustment for covariates. All analyses were first based on all post-SEA children and again on only the post-SEA full sibling children. The results are summarized in Tables 8-31 through 8-33.

Table 8-31

P-Value Summary of Post-SEA Initial Dioxin Analyses (Model 1) of Specific Delays in Development and Hyperkinetic Syndrome of Childhood (Children of Ranch Hands)

a) All Children

Anomaly	Unadjusted D>10 ppt	Unadjusted D>5 ppt	Adjusted D>10 ppt	Adjusted D>5 ppt
Specific Delays in Development	NS	NS	NS	NS
Hyperkinetic Syndrome of Childhood	NS	NS	NS	NS

b) Full Siblings

Anomaly	Unadjusted D>10 ppt	Unadjusted D>5 ppt	Adjusted D>10 ppt	Adjusted D>5 ppt
Specific Delays in Development	NS	NS	NS	NS
Hyperkinetic Syndrome of Childhood	NS	NS*	NS	0.053

Table 8-32

P-Value Summary of Post-SEA Current Dioxin and Time Analyses (Model 2) of Specific Delays in Development and Hyperkinetic Syndrome of Childhood (Children of Ranch Hands)

a) All Children

Unadjusted

Anomaly	D>10 ppt Dioxin by Time	D>10 ppt Time Since SEA (years) ≤18.6	D>10 ppt Time Since SEA (years) >18.6	D>5 ppt Dioxin by Time	D>5 ppt Time Since SEA (years) ≤18.6	D>5 ppt Time Since SEA (years) >18.6
Specific Delays in Development	NS	NS	NS	NS	NS	NS
Hyperkinetic Syndrome of Childhood	NS*	NS	NS	NS	NS	NS*

b) Full Siblings

Unadjusted

Anomaly	D>10 ppt Dioxin by Time	D>10 ppt Time Since SEA (years) ≤18.6	D>10 ppt Time Since SEA (years) >18.6	D>5 ppt Dioxin by Time	D>5 ppt Time Since SEA (years) ≤18.6	D>5 ppt Time Since SEA (years) >18.6
Specific Delays in Development	NS	NS	NS	NS	NS	NS
Hyperkinetic Syndrome of Childhood	NS*	NS	NS	NS	NS	NS*

c) All Children

Adjusted

Anomaly	D>10 ppt Dioxin by Time	D>10 ppt Time Since SEA (years) ≤18.6	D>10 ppt Time Since SEA (years) >18.6	D>5 ppt Dioxin by Time	D>5 ppt Time Since SEA (years) ≤18.6	D>5 ppt Time Since SEA (years) >18.6
Specific Delays in Development	NS	NS	NS	NS	NS	NS
Hyperkinetic Syndrome of Childhood	NS	NS	NS	NS	NS	NS

Table 8-32 (Continued)

d) Full Siblings

Anomaly	Adjusted D>10 ppt Dioxin by Time	Adjusted D>10 ppt Time Since SEA (years) ≤18.6	Adjusted D>10 ppt Time Since SEA (years) >18.6	Adjusted D>5 ppt Dioxin by Time	Adjusted D>5 ppt Time Since SEA (years) ≤18.6	Adjusted D>5 ppt Time Since SEA (years) >18.6
Specific Delays in Development	NS	NS	NS	NS	NS	NS
Hyperkinetic Syndrome of Childhood	NS	NS	NS	NS	NS	NS*

Table 8-33

P-Value Summary of Post-SEA Categorized Current Dioxin Analyses (Model 3) of Specific Delays in Development and Hyperkinetic Syndrome of Childhood (Children of Ranch Hands and Comparisons)

a) All Children

Anomaly	All	Unadjusted Contrasts with Background Unknown	Low	High
Specific Delays in Development	NS	NS	NS*	NS
Hyperkinetic Syndrome of Childhood	NS	NS	NS	NS

b) All Children

Anomaly	All	Adjusted Contrasts with Background Unknown	Low	High
Specific Delays in Development	NS	NS	0.042	NS
Hyperkinetic Syndrome of Childhood	NS	NS	NS	NS

Table 8-33 (Continued)

c) Full Siblings

Unadjusted

Anomaly	All	Contrasts with Background Unknown	Low	High
Specific Delays in Development	NS	NS	NS	NS
Hyperkinetic Syndrome of Childhood	NS	NS	NS	NS

d) Full Siblings

Adjusted

Anomaly	All	Contrasts with Background Unknown	Low	High
Specific Delays in Development	****	****	****	****
Hyperkinetic Syndrome of Childhood	NS	NS	NS	NS

Pre-post SEA analyses of hyperkinetic syndrome of childhood were entirely negative. Unadjusted Model 1 and 2 analyses of specific delays in development found significant associations but these were not supportive of a hypotheses that dioxin is adversely associated with delays in development; the corresponding adjusted analyses were negative. The Model 1 findings were caused by a reversal of pre-SEA and post-SEA trends with dioxin; the pre-SEA rates were increasing and the post-SEA rates decreased or did not increase with dioxin. The Model 2 finding was caused by high post-SEA rates of delays in development in children of Ranch Hands with intermediate dioxin levels and low rates in children of Ranch Hands with high dioxin levels. These patterns are not consistent with the expected dose-response, are inconsistent with each other and are most likely chance occurrences.

Analyses of post-SEA hyperkinetic syndrome of childhood found one significant association in an adjusted Model 1 analysis restricted to full sibling children. This finding was caused by a decreasing rate of hyperkinetic syndrome with dioxin in children of Ranch Hands having more than 5 ppt current dioxin. This finding is opposite to the expected dose-response and is most likely due to chance.

Analyses of post-SEA specific delays in development found one significant association in an adjusted Model 3 analysis. This finding was caused by the rate of delays in development being higher in children of Ranch Hands in the Low dioxin category than in children of Comparisons in the Background category. The rate in children of Ranch Hands in the High dioxin category was not significantly different from the rate in children of Comparisons in the Background category.

A significant interaction with the father's age at the time of birth of the child and the time of conception relative to the father's SEA duty was found in a Model 3 analysis of specific delays in development. This interaction was caused by a significantly high rate in children of Ranch Hands in the Low dioxin category 30 years of age or younger and with the time of conception within 4 years of the father's departure from SEA as compared with the rate in corresponding children of Comparisons in the Background category. Analyses within the other 3 strata determined by the father's age and the time of conception were negative.

These findings are weak, inconsistent and sometimes opposite to the expected dose response. They are therefore not supportive of a hypothesis of an adverse association between dioxin and delays in development or hyperkinetic syndrome. There was insufficient data to assess the association between dioxin and the other 12 anomalies and 2 developmental disorders considered in this chapter.

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_2(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_2(Initial Dioxin)

Ranch Hands - Log_2(Initial) - Unadjusted

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		

Ranch Hands - Log_2(Initial) - Adjusted

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 - Log_2(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: Log_2(Current Dioxin), Time

Ranch Hands - Log_2(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time Since SEA (years)	Anomaly (No./n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
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 - Log_2(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=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 - Log_2(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: Log_2(Initial Dioxin)

Ranch Hands - Log_2(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 - Log_2(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 - Log2(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: Log_2(Current Dioxin), Time

Ranch Hands - Log_2(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time Since SEA (years)	Anomaly (No./n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
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 - Log_2(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=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 though 9-10.

Table 9-8

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

Sibship	Unadjusted D>10 ppt	Unadjusted D>5 ppt	Adjusted D>10 ppt	Adjusted 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.

10. NEONATAL AND INFANT MORTALITY

10.1 Introduction

A childhood death is called a neonatal death if the child dies within 28 days of birth. The death is called an infant death if the child survives the 28th day but dies within 1 year of birth.

10.2 Pre-post SEA Exposure Analyses

The association between neonatal and infant mortality and dioxin was assessed with Models 1, 2 and 3 without and with restriction to full siblings. Pre-post SEA changes are assessed first, followed by post-SEA assessments of association with dioxin. All rates are expressed per 1000 children.

Neonatal Death (All Children)

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

Without adjustment for covariates (Table 10-1 [a] and [b]), there is no significant variation in the association between neonatal death and initial dioxin with time of conception among children of Ranch Hands having more than 10 ppt (p=0.746) or more than 5 ppt (p=0.746) current dioxin.

Table 10-1

Pre-post SEA Counts and Rates of Neonatal Deaths

Variable: Neonatal Death
Restrictions: All Children of Ranch Hands
Categories: Time of Conception Relative to the Father's Duty in SEA
Model 1: Log_2(Initial Dioxin)

Ranch Hands - Log_2(Initial Dioxin) - Unadjusted

Exposure Restriction	Initial Dioxin	Time of Conception Relative to the Father's Duty in SEA: Pre-SEA n	Pre-SEA Deaths	Pre-SEA Rate	Post-SEA n	Post-SEA Deaths	Post-SEA Rate	p-Value
a) D>10 ppt (n=1208)	Low	249	2	8.0	106	0	0.0	0.746
	Medium	338	7	20.7	245	3	12.2	
	High	113	1	8.8	157	3	19.1	
b) D>5 ppt (n=1748)	Low	286	5	17.5	155	2	12.9	0.746
	Medium	616	8	13.0	308	2	6.5	
	High	156	2	12.8	227	4	17.6	

Neonatal Death (All Children)

Model 2: Children of Ranch Hands - Log_2(Current Dioxin) and Time

Without adjustment for covariates (Table 10-2 [a] and [b]), there is no significant change in the association between neonatal death and current dioxin with time since duty in SEA and time of conception among children of Ranch Hands having more than 10 ppt current dioxin (p=0.712) or more than 5 ppt current dioxin (p=0.780).

Table 10-2

Pre-post SEA Counts and Rates of Neonatal Deaths

Variable: Neonatal Death
Restrictions: All Children of Ranch Hands
Categories: Time of Conception Relative to the Father's Duty in SEA
Model 2: Log_2(Current Dioxin), Time

Ranch Hands - Log_2(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time of Conception	Time Since SEA (years)	Neonatal Death Rate (No./n) Current Dioxin Low	Medium	High	p-Value
a) D>10 ppt (n=1210)	Pre-SEA	≤18.6	7.3 (1/137)	10.9 (2/183)	27.0 (1/37)	0.712
		>18.6	10.5 (1/95)	23.4 (4/171)	12.8 (1/78)	
	Post-SEA	≤18.6	0.0 (0/62)	7.5 (1/134)	0.0 (0/72)	
		>18.6	0.0 (0/40)	37.0 (4/108)	10.8 (1/93)	
b) D>5 ppt (n=1748)	Pre-SEA	≤18.6	19.1 (3/157)	3.2 (1/313)	45.5 (3/66)	0.780
		>18.6	13.3 (2/150)	18.5 (5/270)	9.8 (1/102)	
	Post-SEA	≤18.6	11.1 (1/90)	0.0 (0/174)	9.1 (1/110)	
		>18.6	15.9 (1/63)	7.4 (1/136)	34.2 (4/117)	

Neonatal Death (All Children)

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

Without adjustment for covariates (Table 10-3), there is no significant variation in the overall association between neonatal death and categorized dioxin with time of conception (p=0.860). Furthermore, the associations between neonatal death and time of conception among children of Ranch Hands in the High (p=0.422), Low (p=0.939) and Unknown (p=0.731) categories do not differ significantly from that among children of Comparisons in the Background category.

Table 10-3

Pre-post SEA Counts and Rates of Neonatal Death

Variable: Neonatal Death
Restrictions: All Children of Ranch Hands and Comparisons
Categories: Time of Conception Relative to the Father's Duty in SEA
Model 3: Categorized Current Dioxin

Categorized Current Dioxin - Unadjusted

Time of Conception Relative to the Father's Duty in SEA

Exposure Category	Pre-SEA n	Pre-SEA Deaths	Pre-SEA Rate	Post-SEA n	Post-SEA Deaths	Post-SEA Rate	Odds Ratio	Category Contrast	p-Value
Background	1459	13	8.9	981	4	4.1	0.46	All Exp Categ	0.860
Unknown	582	10	17.2	282	3	10.6	0.62	Unk vs Bkgd	0.731
Low	290	4	13.8	174	1	5.7	0.41	Low vs Bkgd	0.939
High	168	4	23.8	227	5	22.0	0.92	High vs Bkgd	0.422
Total	2499			1664					

Neonatal Death (Full Siblings)

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

Without adjustment for covariates (Table 10-4 [a] and [b]), there is no significant variation in the association between neonatal death and initial dioxin with time of conception among full sibling children of Ranch Hands having more than 10 ppt (p=0.735) or more than 5 ppt (p=0.528) current dioxin.

Table 10-4

Pre-post SEA Counts and Rates of Neonatal Deaths

Variable: Neonatal Death
Restrictions: Full Siblings of Ranch Hands
Categories: Time of Conception Relative to the Father's Duty in SEA
Model 1: Log_2(Initial Dioxin)

Ranch Hands - Log_2(Initial Dioxin) - Unadjusted

Exposure Restriction	Initial Dioxin	Time of Conception Relative to the Father's Duty in SEA: Pre-SEA n	Pre-SEA Deaths	Pre-SEA Rate	Post-SEA n	Post-SEA Deaths	Post-SEA Rate	p-Value
a) D>10 ppt (n=1030)	Low	231	2	8.7	78	0	0.0	0.735
	Medium	276	3	10.9	206	3	14.6	
	High	103	1	9.7	136	2	14.7	
b) D>5 ppt (n=1489)	Low	252	5	19.8	114	2	17.5	0.528
	Medium	545	5	9.2	245	2	8.2	
	High	135	1	7.4	198	3	15.2	

Neonatal Death (Full Siblings)

Model 2: Children of Ranch Hands - Log_2(Current Dioxin) and Time

Without adjustment for covariates (Table 10-5 [a] and [b]), there is no significant change in the association between neonatal death and current dioxin with time since duty in SEA and time of conception among full sibling children of Ranch Hands having more than 10 ppt current dioxin (p=0.415) or more than 5 ppt current dioxin (p=0.402).

Table 10-5

Pre-post SEA Counts and Rates of Neonatal Deaths

Variable: Neonatal Death
Restrictions: Full Siblings of Ranch Hands
Categories: Time of Conception Relative to the Father's Duty in SEA
Model 2: Log_2(Current Dioxin), Time

Ranch Hands - Log_2(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time of Conception	Time Since SEA (years)	Neonatal Death Rate (No./n) Current Dioxin Low	Medium	High	p-Value
a) D>10 ppt (n=1032)	Pre-SEA	≤18.6	8.1 (1/124)	12.9 (2/155)	28.6 (1/35)	0.415
		>18.6	11.8 (1/85)	7.0 (1/143)	0.0 (0/69)	
	Post-SEA	≤18.6	0.0 (0/47)	8.7 (1/115)	0.0 (0/64)	
		>18.6	0.0 (0/28)	43.5 (4/92)	0.0 (0/75)	
b) D>5 ppt (n=1489)	Pre-SEA	≤18.6	23.8 (3/126)	3.6 (1/276)	50.0 (3/60)	0.402
		>18.6	13.8 (2/145)	8.4 (2/237)	0.0 (0/88)	
	Post-SEA	≤18.6	16.9 (1/59)	0.0 (0/144)	10.2 (1/98)	
		>18.6	18.9 (1/53)	9.4 (1/106)	30.9 (3/97)	

Neonatal Death (Full Siblings)

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

Without adjustment for covariates (Table 10-6), there is no significant variation in the overall association between neonatal death and categorized dioxin (p=0.782) with time of conception among full siblings. Furthermore, the association between neonatal death and time of conception among children of Ranch Hands in the High (p=0.475), Low (p=0.426) and Unknown (p=0.457) categories do not differ from that among children of Comparisons in the Background category.

Table 10-6

Pre-post SEA Counts and Rates of Neonatal Death

Variable: Neonatal Death
Restrictions: Full Siblings of Ranch Hands and Comparisons
Categories: Time of Conception Relative to the Father's Duty in SEA
Model 3: Categorized Current Dioxin

Categorized Current Dioxin - Unadjusted

Exposure Category	Time of Conception Relative to the Father's Duty in SEA: Pre-SEA n	Pre-SEA Deaths	Pre-SEA Rate	Post-SEA n	Post-SEA Deaths	Post-SEA Rate	Odds Ratio	Category Contrast	p-Value
Background	1250	12	9.6	812	4	4.9	0.51	All Exp Categ	0.782
Unknown	514	7	13.6	221	3	13.6	1.00	Unk vs Bkgd	0.457
Low	244	1	4.1	148	1	6.8	1.65	Low vs Bkgd	0.426
High	148	3	20.3	195	4	20.5	1.01	High vs Bkgd	0.475
Total	2156			1376					

Infant Death (All Children)

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

Without adjustment for covariates (Table 10-7 [a] and [b]), there is no significant variation in the association between infant death and initial dioxin with time of conception among children of Ranch Hands having more than 10 ppt (p=0.424) or more than 5 ppt (p=0.437).

Table 10-7

Pre-post SEA Counts and Rates of Infant Deaths

Variable: Infant Death
Restrictions: All Children of Ranch Hands
Categories: Time of Conception Relative to the Father's Duty in SEA
Model 1: Log_2(Initial Dioxin)

Ranch Hands - Log_2(Initial Dioxin) - Unadjusted

Exposure Restriction	Initial Dioxin	Time of Conception Relative to the Father's Duty in SEA: Pre-SEA n	Pre-SEA Deaths	Pre-SEA Rate	Post-SEA n	Post-SEA Deaths	Post-SEA Rate	p-Value
a) D>10 ppt (n=1192)	Low	247	1	4.0	106	1	9.4	0.424
	Medium	331	2	6.0	242	1	4.1	
	High	112	2	17.9	154	1	6.5	
b) D>5 ppt (n=1725)	Low	281	2	7.1	153	1	6.5	0.437
	Medium	608	2	3.3	306	2	6.5	
	High	154	3	19.5	223	1	4.5	

Infant Death (All Children)

Model 2: Children of Ranch Hands - Log_2(Current Dioxin) and Time

Without adjustment for covariates (Table 10-8 [a] and [b]), there is no significant change in the association between infant death and current dioxin and time since duty in SEA with time of conception among children of Ranch Hands having more than 10 ppt current dioxin (p=0.576) or more than 5 ppt current dioxin (p=0.738).

Table 10-8

Pre-post SEA Counts and Rates of Infant Deaths

Variable: Infant Death
Restrictions: All Children of Ranch Hands
Categories: Time of Conception Relative to the Father's Duty in SEA
Model 2: Log_2(Current Dioxin), Time

Ranch Hands - Log_2(Current Dioxin), Time - Unadjusted

Exposure Restriction	Time of Conception	Time Since SEA (years)	Infant Death Rate (No./n) Current Dioxin Low	Medium	High	p-Value
a) D>10 ppt (n=1194)	Pre-SEA	≤18.6	7.4 (1/136)	0.0 (0/181)	0.0 (0/36)	0.576
		>18.6	0.0 (0/94)	12.0 (2/167)	26.0 (2/77)	
	Post-SEA	≤18.6	0.0 (0/62)	0.0 (0/133)	0.0 (0/72)	
		>18.6	25.0 (1/40)	9.6 (1/104)	10.9 (1/92)	
b) D>5 ppt (n=1725)	Pre-SEA	≤18.6	6.5 (1/154)	3.2 (1/312)	0.0 (0/63)	0.738
		>18.6	6.8 (1/148)	3.8 (1/265)	29.7 (3/101)	
	Post-SEA	≤18.6	11.2 (1/89)	0.0 (0/174)	0.0 (0/109)	
		>18.6	0.0 (0/62)	14.8 (2/135)	8.8 (1/113)	