Infant Death (All Children)

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

Without adjustment for covariates (Table 10-9), there is no significant variation in the association between infant death and categorized dioxin with time of conception (p=0.696). Furthermore, the associations between infant death and time of conception among children of Ranch Hands in the High (p=0.664), Low (p=0.498) and Unknown (p=0.661) categories does not differ significantly from that among children of Comparisons in the Background category.

Table 10-9

Pre-post SEA Counts and Rates of Infant Death

Variable: Infant 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	1446	3	2.1	977	1	1.0	0.49	All Exp Categ	0.696
Unknown	572	2	3.5	279	1	3.6	1.03	Unk vs Bkgd	0.661
Low	286	1	3.5	173	1	5.8	1.66	Low vs Bkgd	0.498
High	164	3	18.3	222	1	4.5	0.24	High vs Bkgd	0.664
Total	2468			1651					

Infant Death (Full Siblings)

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

There is insufficient data (Table 10-10) to assess the significance of variation in the association between infant death and initial dioxin with time of conception among full sibling children of Ranch Hands.

Table 10-10

Pre-post SEA Counts and Rates of Infant Deaths

Variable: Infant 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=1019)	Low	229	1	4.4	78	1	12.8	No analysis, only 5 deaths total
	Medium	273	2	7.3	203	0	0.0	
	High	102	1	9.8	134	0	0.0	
b) D>5 ppt (n=1471)	Low	247	2	8.1	112	1	8.9	No analysis, only 8 deaths total
	Medium	540	2	3.7	243	1	4.1	
	High	134	2	14.9	195	0	0.0	

Infant Death (Full Siblings)

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

There is insufficient data (Table 10-11) to assess the significance of variation in the association between infant death and current dioxin with time of conception among full sibling children of Ranch Hands.

Table 10-11

Pre-post SEA Counts and Rates of Infant Deaths

Variable: Infant 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)	Infant Death Rate (No./n) Current Dioxin Low	Medium	High	p-Value
a) D>10 ppt (n=1021)	Pre-SEA	≤18.6	8.1 (1/123)	0.0 (0/153)	0.0 (0/34)	No analysis, only 5 deaths total
		>18.6	0.0 (0/84)	14.1 (2/142)	14.5 (1/69)	
	Post-SEA	≤18.6	0.0 (0/47)	0.0 (0/114)	0.0 (0/64)	
		>18.6	35.7 (1/28)	0.0 (0/88)	0.0 (0/75)	
b) D>5 ppt (n=1471)	Pre-SEA	≤18.6	8.1 (1/123)	3.6 (1/275)	0.0 (0/57)	No analysis, only 8 deaths total
		>18.6	7.0 (1/143)	4.3 (1/235)	22.7 (2/88)	
	Post-SEA	≤18.6	17.2 (1/58)	0.0 (0/144)	0.0 (0/97)	
		>18.6	0.0 (0/52)	9.5 (1/105)	0.0 (0/94)	

Infant Death (Full Siblings)

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

There is insufficient data (Table 10-12) to assess the significance of variation in the association between infant death and categorized current dioxin among full sibling children.

Table 10-12

Pre-post SEA Counts and Rates of Infant Death

Variable: Infant 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

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	1238	1	0.8	808	1	1.2	1.53	All Exp Categ	No analy-
Unknown	507	2	3.9	218	1	4.6	1.16	Unk vs Bkgd	sis, 8
Low	243	1	4.1	147	0	0.0	--	Low vs Bkgd	deaths
High	145	2	13.8	191	0	0.0	--	High vs Bkgd	total
Total	2133			1364					

10.3 Post-SEA Exposure Analyses

The association between neonatal and infant mortality and dioxin was assessed in post-SEA children with Models 1, 2 and 3. All analysis were carried out without and then with adjustment for covariates. Each analysis was first conducted without and then with restriction to full sibling children. The results are given in Tables 10-13 through 10-24.

Neonatal Death (All Children)

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

Without adjustment for covariates (Table 10-13 [a] and [b]), there is no significant association between neonatal death and initial dioxin among full sibling children of Ranch Hands having more than 10 ppt (p=0.350) or more than 5 ppt (p=0.489) current dioxin.

There is insufficient data (Table 10-13 [c] and [d]) to assess the significance of the association between neonatal death and initial dioxin with adjustment for covariates.

Table 10-13

Post-SEA Counts and Rates of Neonatal Death

Variable: Neonatal Death
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	Neonatal Deaths Number	Neonatal Deaths Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=508)	Low	106	0	0.0	0.73(0.38,1.40)	0.350
	Medium	245	3	12.2		
	High	157	3	19.1		
b) D>5 ppt (n=690)	Low	155	2	12.9	0.84(0.52,1.36)	0.489
	Medium	308	2	6.5		
	High	227	4	17.6		

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)	No adjusted analysis, only 6 deaths total		
d) D>5 ppt (n=616)	No adjusted analysis, only 8 deaths total		

Neonatal Death (All Children)

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

There is not sufficient data (Table 10-14) to assess the significance of variation in the association between neonatal death and current dioxin with time since duty in SEA without or with adjustment for covariates.

Table 10-14

Post-SEA Counts and Rates of Neonatal Death

Variable: Neonatal Death
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 Death Rate (No./n) Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=509)						
	≤18.6	0.0 (0/62)	7.5 (1/134)	0.0 (0/72)	No analysis, only 6 deaths total	
	>18.6	0.0 (0/40)	37.0 (4/108)	10.8 (1/93)		
b) D>5 ppt (n=690)						
	≤18.6	11.1 (1/90)	0.0 (0/174)	9.1 (1/110)	No analysis, only 8 deaths total	
	>18.6	15.9 (1/63)	7.4 (1/136)	34.2 (4/117)		

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)	No adjusted analysis, only 6 deaths total			
d) D>5 ppt (n=616)	No adjusted analysis, only 8 deaths total			

Neonatal Death (All Children)

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

Without adjustment for covariates (Table 10-15 [a]), there is a significant overall association between neonatal death and categorized current dioxin (p=0.045). The neonatal death rate among children of Ranch Hands in the High category is significantly greater than the rate in children of Comparisons in the Background category (p=0.005). The neonatal death rates in children of Ranch Hands in the Low (p=0.757) and Unknown (p=0.191) categories are not significantly different from the rate in children of Comparisons in the Background category.

There is insufficient data (Table 10-15 [b]) to assess the significance of the association between neonatal death and categorized current dioxin with adjustment for covariates.

Table 10-15

Post-SEA Counts and Rates of Neonatal death

Variable: Neonatal Death
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	Neonatal Death Number	Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	981	4	4.1	All Exp Categ		0.045
Unknown	282	3	10.6	Unk vs Bkgd	2.63(0.62,11.2)	0.191
Low	174	1	5.7	Low vs Bkgd	1.41(0.16,12.7)	0.757
High	227	5	22.0	High vs Bkgd	5.50(1.46,20.7)	0.005
Total	1664					

b) Adjusted

Exposure Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	843	All Exp Categ	No adjusted analysis, only 13 deaths total		
Unknown	246	Unk vs Bkgd			
Low	156	Low vs Bkgd			
High	203	High vs Bkgd			
Total	1448				

Neonatal Death (Full Siblings)

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

Without adjustment for covariates (Table 10-16 [a] and [b]), there is no significant association between neonatal death and initial dioxin among full sibling children of Ranch Hands having more than 10 ppt (p=0.684) or more than 5 ppt (p=0.959) current dioxin.

There is insufficient data (Table 10-16 [c] and [d]) to assess the significance of the association between neonatal death and initial dioxin with adjustment for covariates among full sibling children of Ranch Hands.

Table 10-16

Post-SEA Counts and Rates of Neonatal Death

Variable: Neonatal Death
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	Neonatal Death Number	Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=420)	Low	78	0	0.0	0.86(0.42,1.77)	0.684
	Medium	206	3	14.6		
	High	136	2	14.7		
b) D>5 ppt (n=557)	Low	114	2	17.5	0.99(0.58,1.67)	0.959
	Medium	245	2	8.2		
	High	198	3	15.2		

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)	No adjusted analysis, only 5 deaths total		
d) D>5 ppt (n=513)	No adjusted analysis, only 7 deaths total		

Neonatal Death (Full Siblings)

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

There is insufficient data (Table 10-17) to assess the significance of variation in the association between neonatal deaths and current dioxin with time since duty in SEA without or with adjustment for covariates among full sibling children of Ranch Hands.

Table 10-17

Post-SEA Counts and Rates of Neonatal Death

Variable: Neonatal Death
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 Death Rate (No./n) Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=421)						
	≤18.6	0.0 (0/47)	8.7 (1/115)	0.0 (0/64)	No analysis, only 5 deaths total	
	>18.6	0.0 (0/28)	43.5 (4/92)	0.0 (0/75)		
b) D>5 ppt (n=557)						
	≤18.6	16.9 (1/59)	0.0 (0/144)	10.2 (1/98)	No analysis, only 7 deaths total	
	>18.6	18.9 (1/53)	9.4 (1/106)	30.9 (3/97)		

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)	No adjusted analysis, only 5 deaths total			
d) D>5 ppt (n=513)	No adjusted analysis, only 7 deaths total			

Neonatal Death (Full Siblings)

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

Without adjustment for covariates (Table 10-18 [a]), there is no significant overall association between neonatal death and categorized current dioxin among full siblings (p=0.161). The neonatal death rate in children of Ranch Hands in the High category is significantly greater than the rate in the children of Comparisons in the Background category (p=0.028). The death rates in children of Ranch Hands in the Low (p=0.776) and Unknown (p=0.165) categories are not significantly different from the rate in children of Comparisons in the Background category.

There is insufficient data (Table 10-18 [b]) to assess the significance of the association between neonatal death and categorized current dioxin with adjustment for covariates among full sibling children.

Table 10-18

Post-SEA Counts and Rates of Neonatal Death

Variable: Neonatal Death
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	Neonatal Death Number	Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	812	4	4.9	All Exp Categ		0.161
Unknown	221	3	13.6	Unk vs Bkgd	2.78(0.62,12.5)	0.165
Low	148	1	6.8	Low vs Bkgd	1.37(0.15,12.4)	0.776
High	195	4	20.5	High vs Bkgd	4.23(1.05,17.1)	0.028
Total	1376					

b) Adjusted

Exposure Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	715	All Exp Categ	No adjusted analysis, only 12 deaths total		
Unknown	199	Unk vs Bkgd			
Low	137	Low vs Bkgd			
High	180	High vs Bkgd			
Total	1231				

Infant Death (All Children)

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

Without adjustment for covariates (Table 10-19 [a] and [b]), there is no significant association between infant death and initial dioxin among children of Ranch Hands having more than 10 ppt (p=0.921) or more than 5 ppt (p=0.993) current dioxin.

There is insufficient data (Table 10-19 [c] and [d]) to assess the significance of the association between infant death and initial dioxin with adjustment for covariates.

Table 10-19

Post-SEA Counts and Rates of Infant Death

Variable: Infant Death
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	Infant Death Number	Infant Death Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=502)	Low	106	1	9.4	0.95(0.37,2.46)	0.921
	Medium	242	1	4.1		
	High	154	1	6.5		
b) D>5 ppt (n=682)	Low	153	1	6.5	1.00(0.50,2.02)	0.993
	Medium	306	2	6.5		
	High	223	1	4.5		

Ranch Hands - Log_2(Initial Dioxin) - Adjusted

Exposure Restriction	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=452)	No adjusted analysis, only 3 death total		
d) D>5 ppt (n=609)	No adjusted analysis, only 4 deaths total		

Infant Death (All Children)

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

There is insufficient data (Table 10-20) to assess the significance of variation in the association between infant death and current dioxin with time since duty in SEA without or with adjustment for covariates.

Table 10-20

Post-SEA Counts and Rates of Infant Death

Variable: Infant Death
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 Death Rate (No./n) Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=503)						
	≤18.6	0.0 (0/62)	0.0 (0/133)	0.0 (0/72)	No analysis, only 3 deaths total	
	>18.6	25.0 (1/40)	9.6 (1/104)	10.9 (1/92)		
b) D>5 ppt (n=682)						
	≤18.6	11.2 (1/89)	0.0 (0/174)	0.0 (0/109)	No analysis, only 4 deaths total	
	>18.6	0.0 (0/62)	14.8 (2/135)	8.8 (1/113)		

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=452)	No adjusted analysis, only 3 deaths total			
d) D>5 ppt (n=609)	No adjusted analysis, only 4 deaths total			

Infant Death (All Children)

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

There is insufficient data (Table 10-21) to assess the significance of the association between infant death and categorized current dioxin without or with adjustment for covariates.

Table 10-21

Post-SEA Counts and Rates of Infant Death

Variable: Infant Death
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	Infant Death Number	Infant Death Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	977	1	1.0	All Exp Categ	No analysis, only 4	
Unknown	279	1	3.6	Unk vs Bkgd	deaths total	
Low	173	1	5.8	Low vs Bkgd		
High	222	1	4.5	High vs Bkgd		
Total	1651					

b) Adjusted

Exposure Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	839	All Exp Categ	No adjusted analysis, only 4		
Unknown	244	Unk vs Bkgd	deaths total		
Low	155	Low vs Bkgd			
High	198	High vs Bkgd			
Total	1436				

Infant Death (Full Siblings)

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

There is insufficient data (Table 10-22) to assess the significance of the association between infant death and initial dioxin without or with adjustment for covariates among full sibling children of Ranch Hands.

Table 10-22

Post-SEA Counts and Rates of Infant Death

Variable: Infant Death
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	Infant Death Number	Infant Death Rate	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=415)	Low	78	1	12.8	No analysis, only 1 death total	
	Medium	203	0	0.0		
	High	134	0	0.0		
b) D>5 ppt (n=550)	Low	112	1	8.9	No analysis, only 2 deaths total	
	Medium	243	1	4.1		
	High	195	0	0.0		

Ranch Hands - Log_2(Initial Dioxin) - Adjusted

Exposure Restriction	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) D>10 ppt (n=385)	No adjusted analysis, only 1 death total		
d) D>5 ppt (n=507)	No adjusted analysis, only 2 deaths total		

Infant death (Full Siblings)

Model 2: Children of Ranch Hands - Log_2(current dioxin) and time

There is insufficient data (Table 10-23) to assess the significance of variation in the association between infant deaths and current dioxin with time since duty in SEA without or with adjustment for covariates among full sibling children of Ranch Hands.

Table 10-23

Post-SEA Counts and Rates of Infant Death

Variable: Infant Death
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 Death Rate (No./n) Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
a) D>10 ppt (n=416)						
	≤18.6	0.0 (0/47)	0.0 (0/114)	0.0 (0/64)	No analysis, only 1 death total	
	>18.6	35.7 (1/28)	0.0 (0/88)	0.0 (0/75)		
b) D>5 ppt (n=550)						
	≤18.6	17.2 (1/58)	0.0 (0/144)	0.0 (0/97)	No analysis, only 2 deaths total	
	>18.6	0.0 (0/52)	9.5 (1/105)	0.0 (0/94)		

Table 10-23 (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=386)	No adjusted analysis, only 1 death total			
d) D>5 ppt (n=507)	No adjusted analysis, only 2 deaths total			

Infant Death (Full Siblings)

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

There is insufficient data (Table 10-24) to assess the significance of the association between infant death and categorized current dioxin without or with adjustment for covariates among full sibling children.

Table 10-24

Post-SEA Counts and Rates of Infant Death

Variable: Infant Death
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	Infant Number	Death Rate	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	808	1	1.2	All Exp Categ	No analysis, only 2	
Unknown	218	1	4.6	Unk vs Bkgd	deaths total	
Low	147	0	0.0	Low vs Bkgd		
High	191	0	0.0	High vs Bkgd		
Total	1364					

Table 10-24 (Continued)

b) Adjusted

Exposure Category	n	Category Contrast	Est. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	711	All Exp Categ	No adjusted analysis, only 2 deaths total		
Unknown	197	Unk vs Bkgd			
Low	136	Low vs Bkgd			
High	176	High vs Bkgd			
Total	1220				

10.4 Conclusion

Neonatal and infant death were examined for possible associations with dioxin using Models 1, 2 and 3. The first series of analyses were directed at changes in the association between risk of death and dioxin with time of conception relative to the father's duty in SEA. These pre-post SEA analyses are summarized in Tables 10-25 through 10-27.

Table 10-25

P-Value Summary of Initial Dioxin (Model 1) Pre-Post SEA Analyses of Neonatal and Infant Death

Outcome	Sibship Restriction	D>10 ppt	D>5 ppt
Neonatal Death	All Children	NS	NS
	Full Siblings	NS	NS
Infant Death	All Children	NS	NS
	Full Siblings	--	--

Table 10-26

P-Value Summary of Current Dioxin and Time (Model 2) Pre-Post SEA Analyses of Neonatal and Infant Death

a) All Children

Outcome	Unadjusted D>10 ppt	Unadjusted D>5 ppt
Neonatal Death	NS	NS
Infant Death	NS	NS

b Full Siblings

Outcome	Unadjusted D>10 ppt	Unadjusted D>5 ppt
Neonatal Death	NS	NS
Infant Death	--	--

Table 10-27

P-Value Summary of Categorized Dioxin (Model 3) Pre-Post SEA Analyses of Neonatal and Infant Death

a) All Children

Outcome	All	Contrasts with Background: Unknown	Low	High
Neonatal Death	NS	NS	NS	NS
Infant Death	NS	NS	NS	NS

b) Full Siblings

Outcome	All	Contrasts with Background: Unknown	Low	High
Neonatal Death	NS	NS	NS	NS
Infant Death	--	--	--	--

These data were generally too sparse to carry out all analyses. When the data were sufficient for analysis, no significant variation in the association between neonatal and infant mortality and dioxin was found.

Assessments of the association between neonatal and infant death and dioxin in post-SEA births were also carried out. The results are summarized in Tables 10-28 through 10-30.

Table 10-28

P-Value Summary of Initial Dioxin (Model 1) Post-SEA Analyses of Neonatal and Infant Death

a) Unadjusted

Outcome	Sibship Restriction	D>10 ppt	D>5 ppt
Neonatal Death	All Children	NS	NS
	Full Siblings	NS	NS
Infant Death	All Children	NS	NS
	Full Siblings	--	--

b) Adjusted

Outcome	Sibship Restriction	D>10 ppt	D>5 ppt
Neonatal Death	All Children	--	--
	Full Siblings	--	--
Infant Death	All Children	--	--
	Full Siblings	--	--

Table 10-29

P-Value Summary of Current Dioxin and Time (Model 2) Post-SEA Analyses of Neonatal and Infant Death

a) Unadjusted

		D>10 ppt			D>5 ppt		
			Time Since SEA (years)			Time Since SEA (years)	
Outcome	Sibship Restriction	Dioxin by Time	≤18.6	>18.6	Dioxin by Time	≤18.6	>18.6
Neonatal	All Children	--	--	--	--	--	--
	Full Siblings	--	--	--	--	--	--
Infant	All Children	--	--	--	--	--	--
	Full Siblings	--	--	--	--	--	--

Table 10-29 (Continued)

b) Adjusted

Outcome	Sibship Restriction	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
Neonatal	All Children	--	--	--	--	--	--
	Full Siblings	--	--	--	--	--	--
Infant	All Children	--	--	--	--	--	--
	Full Siblings	--	--	--	--	--	--

Table 10-30

P-Value Summary of Categorized Current Dioxin (Model 3) Post-SEA Analyses of Neonatal and Infant Death

a) Unadjusted

Outcome	Sibship Restriction	All	Contrasts with Background: Unknown	Low	High
Neonatal Death	All Children	0.045	NS	NS	0.005
	Full Siblings	NS	NS	NS	0.028
Infant Death	All Children	--	--	--	--
	Full Siblings	--	--	--	--

b) Adjusted

Outcome	Sibship Restriction	All	Contrasts with Background: Unknown	Low	High
Neonatal Death	All Children	--	--	--	--
	Full Siblings	--	--	--	--
Infant Death	All Children	--	--	--	--
	Full Siblings	--	--	--	--

Analyses of post-SEA infant death were either negative or could not be carried out due to insufficient data. Analyses of post-SEA neonatal death found significant associations in two Model 3 analyses. Both of these findings were caused by the rate of post-SEA neonatal death being higher in children of Ranch Hands in the High dioxin category than in children of Comparisons in the Background category. However, the corresponding pre-post

SEA data show that pre-SEA children of Ranch Hands in the High category also had a higher rate than pre-SEA children in the Background category. Therefore, these finding appear due to chance rather than to paternal dioxin exposure.

These analyses were generally negative and the two significant associations found in analyses of neonatal death most likely chance occurrences. We conclude that there is no association between dioxin and infant or neonatal mortality.

11. BIAS INVESTIGATION

11.1 Introduction

Any study of reproductive outcomes will produce biased results if children are misclassified according to birth defect status. In this study, we addressed this source of bias through medical record verification of every child, regardless of parental opinion regarding birth defects. The verification process has eliminated the possibility of reporting bias. Nevertheless, bias may occur due to differential verification of the children. Differential verification might occur if, as a result of media publicity, Ranch Hand parents asked physicians to look for birth defects during routine visits, actively sought medical opinion regarding potential defects, or directed Air Force investigators to medical records that documented defects in favor of those records that did not document defects, while Comparison parents did not exhibit this behavior. Differential verification of this kind would not affect analyses involving only Ranch Hands (Models 1 and 2) because all Ranch Hands were blinded to their dioxin result prior to and during the verification process. Differential verifiability might, however, affect analyses based on Model 3. In this section rates are expressed per 1000 children.

11.2 Analysis

Four sources were used, in various combinations, to verify conception outcome and birth defect status. They were: birth certificates, newborn clinic records, health records and death certificates. Counts of children with verified defects fathered by participants included in Models 1, 2 or 3 according to these sources and their combinations are shown in Table 11-1, categorized by the father's group membership (Ranch Hand, Comparison) and time of conception relative to the father's duty in SEA (pre-SEA, post-SEA).

Table 11-1

Counts of Verified Defective Children Included in Models 1, 2 or 3 by Source of Record, Fathers Group Membership and Time of Conception

Source	Time of Conception Relative to the Father's Duty in SEA: Pre-SEA Ranch Hand (n=1283)	Pre-SEA Comparison (n=1459)	Post-SEA Ranch Hand (n=791)	Post-SEA Comparison (n=981)
Birth certificate only	0	0	0	0
Death certificate only	0	1	0	0
Birth and death certificates	0	0	0	0
Birth and death certificates and health records	1	0	0	0
Death certificate and newborn clinic	0	0	0	0
Death certificate and newborn clinic and health records	0	0	0	0
Death certificate and birth certificate and newborn clinic	1	0	0	0
Death certificate and birth certificate and newborn clinic and health records	3	0	0	0
Birth certificate and health records	31	48	26	27
Newborn clinic only	1	3	3	3
Newborn clinic and health records	3	5	11	17
Birth certificate and newborn clinic	19	22	28	28
Birth certificate and newborn clinic and health records	68	58	92	103
Health records only	5	9	7	12
Death certificate and health records	0	1	0	0
Death certificate and birth certificate and newborn clinic and health records plus death certificate	0	1	0	0
Birth certificate and newborn clinic and health records plus death certificate and birth certificate and newborn clinic	1	1	0	1
Birth certificate and death certificate plus death certificate	0	0	1	0
Birth certificate and death certificate and health records plus birth certificate and newborn certificate	0	1	0	0

Table 11-1 (Continued)

Source	Time of Conception Relative to the Father's Duty in SEA: Pre-SEA Ranch Hand (n=1283)	Pre-SEA Comparison (n=1459)	Post-SEA Ranch Hand (n=791)	Post-SEA Comparison (n=981)
Birth certificate and newborn clinic and health records and death certificate plus birth certificate and newborn clinic	1	0	0	0
Birth certificate and newborn clinic and health records plus birth certificate and newborn clinic and health records and death certificate	1	1	0	2
Birth certificate and newborn clinic and health records plus birth certificate and newborn clinic	3	4	7	9
Newborn clinic and health records plus newborn clinic	0	1	0	2
Birth certificate and health records plus death certificate	1	1	0	0
Birth certificate and health records plus health records	0	1	0	0
Birth certificate and health records and death certificate plus birth certificate	0	0	1	0
Birth certificate and newborn clinic and health records plus birth certificate and newborn clinic plus birth certificate and newborn clinic and death certificate	1	0	0	0
Total	140	158	176	204

We assume that parents have no control over the existence or content of birth certificates, newborn clinic records or death certificates. Parents might influence the existence or content of health records, however, through elective health care and pointed requests to physicians to find and annotate birth defects. Hence all combinations of sources involving health records might be subject to this bias, although the phenomenon might be expected to occur most often in children with no other corroborating source (health records only) because, presumably, the parents would know that the birth defect was already noted on the birth certificate or in the newborn clinic records and would therefore not be inclined to seek further documentation from a physician.

Pre-SEA and Post-SEA counts and rates are presented in Table 11-2 and odds ratios and associated test statistics are presented in Table 11-3 for all sources involving health records and for health records only.

Table 11-2

Pre-SEA and Post-SEA Counts and Rates by Source of Record and the Father's Group Membership Among Children Whose Father Entered any of Model 1, 2 or 3 Analyses

	Time of Conception Relative to the Father's Duty in SEA			
	Pre-SEA		Post-SEA	
Source	Ranch Hand Count(Rate)	Comparison Count(Rate)	Ranch Hand Count(Rate)	Comparison Count(Rate)
All combinations of sources involving health records	119 (92.8)	132 (90.5)	144 (182.0)	173 (176.4)
Health records only	5 (3.9)	9 (6.2)	7 (8.8)	12 (12.2)

Without adjustment for covariates (Table 11-3), there is no significant variation in the association between source of record (all combinations of sources involving health records versus all other sources) and the father's group membership (Ranch Hand, Comparison) with time of conception relative to duty in SEA (p=0.950). Furthermore, there is no significant association between source of record and father's group membership among pre-SEA (p=0.836) or among post-SEA (p=0.756) conceptions. After restriction to health records only, there is no significant variation in the association between source of record and the father's group membership with time of conception relative to duty in SEA (pre-SEA odds ratio=0.63, post-SEA odds ratio=0.72, p=0.855). There is no significant association between source of record and the father's group membership among pre-SEA (p=0.405) or post-SEA (p=0.492) children.

Table 11-3

Pre-SEA and Post-SEA Odds Ratios Relating Source of Record and the Father's Group Membership Among Children Whose Father Entered any of Model 1, 2 or 3 Analyses

Source	Time of Conception Relative to the Father's Duty in SEA: Pre-SEA Odds Ratio	Pre-SEA p-value	Post-SEA Odds Ratio	Post-SEA p-value	Test for Equality of Odds Ratios p-value
All combinations of sources involving health records	1.03	0.836	1.04	0.756	0.950
Health records only	0.63	0.405	0.72	0.492	0.855

Verification bias, if it exists, might be most prominent in children who were at least one month old when the Agent Orange publicity began to peak in early 1978. Hence, the significance of the association between source of record and the father's group membership was assessed with the source of record being any combination involving health records and health records only for children aged one month or older on 1 January 1978 (born on or before 1 December 1977). The results are summarized in Table 11-4 and 11-5.

Table 11-4

Pre-SEA and Post-SEA Counts and Rates by Source of Record and the Father's Group Membership Among Children Aged One Month or Older on 1 January 1978 and Whose Father Entered any of Model 1, 2 or 3 Analyses

	Time of Conception Relative to the Father's Duty in SEA			
	Pre-SEA		Post-SEA	
Source	Ranch Hand Count(Rate)	Comparison Count(Rate)	Ranch Hand Count(Rate)	Comparison Count(Rate)
All combinations of sources involving health records	119 (92.3)	132 (90.5)	105 (173.8)	122 (168.5)
Health records only	5 (3.9)	9 (6.2)	5 (8.3)	10 (13.8)

Without adjustment for covariates (Table 11-5) and with restriction to children aged one month or older on 1 January 1978, there is no significant variation in the association between source of record (all combinations involving health records versus all other sources) and the father's group membership (Ranch Hand, Comparison) with time of conception relative to duty in SEA (p=0.959). Furthermore, there is no significant association between source of record and the father's group membership among pre-SEA (p=0.836) or among post-SEA (p=0.797) conceptions. After restriction to health records only, there is no significant variation in the association between source of record and the father's group membership with time of conception relative to duty in SEA (pre-SEA odds ratio=0.63, post-SEA odds ratio=0.60, p=0.943). There is no significant association between source of record and the father's group membership among pre-SEA (p=0.405) or post-SEA (p=0.342) children.

Table 11-5

Pre-SEA and Post-SEA Odds Ratios Relating Source of Record and Fathers Group Membership Among Children Aged One Month or Older on 1 January 1978 Whose Father Entered any of Model 1, 2 or 3 Analyses

	Time of Conception Relative to the Father's Duty in SEA				
	Pre-SEA		Post-SEA		Test for Equality of Odds Ratios
Source	Odds Ratio	p-value	Odds Ratio	p-value	p-value
All combinations of sources involving health records	1.03	0.836	1.04	0.797	0.959
Health records only	0.63	0.405	0.60	0.342	0.943

As a final bias assessment, the possibility that children of fathers who gave blood for the dioxin assay might be more or less likely to exhibit birth defects than children of fathers who did not provide blood for the dioxin assay was investigated because only children whose father had a valid serum dioxin result were included in the analyses summarized in this report. To this end, all 6792 verified biologic children of Ranch Hands and Comparisons were classified as having a verified birth defect if the defect was verified and satisfied the CDC definition of total congenital anomaly. The fathers were categorized as assayed or not assayed according to whether they did or did not give blood for the serum dioxin assay (regardless of the result of the assay). These data were further categorized by the father's group (Ranch Hand, Comparison), the time of conception of the child (pre-SEA, post-SEA) and the father's military occupation in SEA (officer, enlisted flyer, enlisted ground personnel). These data are summarized in Table 11-6.

Table 11-6

Cross Classification of 6792 Verified Biologic Children by Birth Defect, Time of Conception and the Father's Assay Status, Group and Military Occupation

a) Children of Fathers Not Assayed for Dioxin

Time of Conception	Father's Occupation	Group	Children with Birth Defects	Total	Rate (per 1000)
Pre-SEA	Officer	RH	18	174	103.4
		C	28	264	106.1
	Enlisted Flyer	RH	10	79	126.6
		C	17	128	132.8
	Enlisted Ground	RH	10	172	58.1
		C	22	264	83.3
Post-SEA	Officer	RH	19	65	292.3
		C	17	154	110.4
	Enlisted Flyer	RH	7	24	291.7
		C	10	36	277.8
	Enlisted Ground	RH	18	118	152.5
		C	25	250	100.0

Table 11-6 (Continued)

b) Children of Fathers Assayed for Dioxin

Time of Conception	Father's Occupation	Group	Children with Birth Defects	Total	Rate (per 1000)
Pre-SEA	Officer	RH	71	678	104.7
		C	104	832	125.0
	Enlisted Flyer	RH	35	301	116.3
		C	35	349	100.3
	Enlisted Ground	RH	40	401	99.8
		C	48	503	95.4
Post-SEA	Officer	RH	33	204	161.8
		C	77	344	223.8
	Enlisted Flyer	RH	25	97	257.7
		C	24	119	201.7
	Enlisted Ground	RH	127	537	236.5
		C	136	699	194.6

A log-linear analysis of these data found significant variation in the association between birth defects and assay status with the father's military occupation in SEA (p=0.008) and no significant variation with the father's group. This interaction is summarized in Table 11-7.

Table 11-7

Birth Defects versus the Father's Assay Status
by the Father's Military Occupation in SEA

a) Children of Fathers Not Assayed for Dioxin

The Father's Occupation	Children with Birth Defects	Total	Rate (per 1000)
Officer	82	657	124.8
Enlisted Flyer	44	267	164.8
Enlisted Ground	75	804	93.3

Table 11-7 (Continued

b) Children of Fathers Assayed for Dioxin

The Father's Occupation	Children with Birth Defects	Total	Rate (per 1000)
Officer	285	2058	138.5
Enlisted Flyer	119	866	137.4
Enlisted Ground	351	2140	164.0

This interaction is primarily due to the difference in birth defect rates in children of enlisted ground personnel who were not assayed (93.3 per 1000) and in children of enlisted ground personnel who were assayed (164.1 per 1000). This difference in rates is statistically significant ($p<0.001$). The rates did not differ significantly for the officer or enlisted flyer occupation.

This rate difference indicates the presence of selection bias; children of fathers who volunteered for the dioxin assay and who were enlisted ground personnel in Vietnam are more likely to have verified birth defects than children of such fathers who did not volunteer. This difference does not detract from the inferences of this report, however, because the rate is higher in children of assayed fathers than in children of unassayed fathers.

11.3 Conclusion

We considered the possibility that Ranch Hand parents actively sought medical opinion regarding birth defects in their children, making birth defects more verifiable in their children than in Comparison children. We found no evidence of this 'verification' bias. We also investigated selection bias for the dioxin assay and found that children of enlisted ground personnel who volunteered for the assay were more likely to have birth defects than children of enlisted ground personnel who did not volunteer. This difference constitutes a selection bias. However, this bias is not detrimental to this report because the birth defect rate was higher in children of assayed fathers than in children of unassayed fathers.

12. CONCLUSION

12.1 Introduction

Fear of cancer in Vietnam veterans and the occurrence of birth defects in their children has driven interest in the Agent Orange issue in veterans, the general public and federal and state legislatures. The Air Force began planning for the Air Force Health Study (AFHS) in late 1978 to evaluate these and other health issues in the group of Air Force veterans who handled and sprayed dioxin-containing herbicides on a daily basis in Southeast Asia (SEA) from 1962 to 1970. Initial physical examinations and questionnaires were performed in 1982, with subsequent evaluations in 1985, 1987 and currently in 1992.

Reproductive outcomes were assessed in the baseline AFHS report published in February 1984. The analyses of reproductive outcomes contained in that report were based on defects reported by the mothers of the children. No verification of those reports were carried out because the necessary medical records were not available at that time. Action was begun in 1985 to locate and obtain records for each conception, regardless of the mother's report. This task involved the collection of medical records on 9,921 conceptions and 8,100 live births.

12.2 Previous Studies

The scientific investigation of the effects of dioxin on the reproductive system has focused primarily on studies of exposed pregnant rodents and their offspring. Studies have identified a range of teratogenic abnormalities in fetuses when the mothers were fed varying amounts of dioxin, but few studies have been done following exposures of the fathers. Only a few studies evaluated the mating behaviors and reproductive success of male rats after exposure to dioxin at levels causing systemic toxicity. Mating behavior, litter size and birth defect rates were not affected by the father's exposure in one study [16], but the mating index decreased, sterility increased and the pregnancy index was normal in a second study [17]. Because of interspecies variability, the applicability of these animal studies directly to humans is in doubt.

All of the studies of reproductive effects of dioxin in humans conducted to date have relied on broad assumptions concerning the degree of dioxin exposure rather than upon direct measurement. Many studies have been no more than case reports of birth defects without any attempt to verify actual dioxin exposure. The birth defect studies conducted by the Government of Australia [18] and by the Centers for Disease Control [15] were unable to classify Vietnam veterans by their actual dioxin levels but only evaluated differences between Vietnam and non-Vietnam veterans, using presence in Vietnam as a surrogate for dioxin exposure. The studies of miscarriage in residents of Alsea, Oregon in 1978 were also unable to determine actual dioxin levels of

individual subjects. In all of these studies, the possibility of exposure misclassification limits the reliability of the results. Some previous studies were limited by small samples as well as lack of direct exposure measurements [19,20]. For example, studies of birth defects subsequent to a 1976 industrial accident in Seveso, Italy found no increased risk of major birth defects in the offspring of dioxin-exposed mothers, but the number of children of mothers with the highest likelihood of exposure was too small to assess specific categories of defects [21].

Recently, researchers have concentrated on the direct effects of dioxin in cultures derived from animal fetal tissue [22-25]. These studies have identified dioxin effects in neurological, palate, and kidney tissues. As in other animal studies, the applicability of these results to paternal human exposure remains debatable.

The study described in this report is the first to combine an accurate direct measurement of paternal dioxin level with documented and verified reproductive outcomes in a population of sufficient size to provide a reasonable opportunity to detect associations between paternal dioxin levels and a range of common reproductive outcomes. This study has good statistical power to detect relative risks of 2 for common birth defects such as musculoskeletal deformities and but no statistical power for relative risks of this order for rare conditions such as chromosomal abnormality or infant death.

The reduction of exposure misclassification and elimination of errors in determining the presence of birth defects has minimized the two most important sources of bias in epidemiologic studies of reproductive outcome. This study evaluates a range of reproductive outcomes including semen abnormalities, inability to conceive, prematurity (birth weight below 2500 grams), birth defects, neonatal and infant death and developmental abnormalities. This is the most comprehensive evaluation of paternal dioxin exposure and reproductive outcomes and, the most thorough accounting of the reproductive health of 1,686 men and the health and development to age 18 of their 4,514 children ever done.

12.3 Statistical Methods and Interpretation

The significance of the association between paternal dioxin level and post-SEA birth defects was assessed, in 12 separate series of analyses, within each of 13 categories of anomalies: total congenital, nervous system, eye, ear face and neck, circulatory system and heart, respiratory system, digestive system, genital, urinary, musculoskeletal, skin, chromosomal and other unspecified defects. Analyses were first conducted on all children and then, to minimize genetic variation, with restriction to full siblings. Within each of these two series, each analysis was carried out first without and then, when possible, with adjustment for covariates. A separate series of analyses, termed pre-post SEA, assessed the dioxin versus outcome after the father's service in Southeast Asia (post-SEA) with adjustment for outcomes which occurred before the father's service in Southeast Asia (pre-SEA).

Three dioxin measures were used: the extrapolated initial dose (Model 1), current dioxin with adjustment for time since departure from SEA (Model 2), and categorized current dioxin (Model 3). The first two of these models were applied only to children of Ranch Hands. The third included children of both Ranch Hands and Comparisons.

Assessment of external consistency is difficult in this study because prior information is weak or nonexistent. Internal consistency checks in this report were based on the following assumptions: (1) a genuine effect might be expressed in more than one birth defect category but not in all birth defect categories and (2) a genuine effect within a birth defect category would not likely be expressed in all subcategories.

Little or no information is available with which to hypothesize the "expected" pattern if dioxin were adversely related to reproductive outcome. Nevertheless, two patterns were considered as the "expected dose-response" if dioxin were adversely associated with reproductive outcome. These were (1) a positive linear association and (2) a nonlinear association in which the highest rates of anomaly occur at intermediate levels of paternal dioxin. The first appears plausible if dioxin is a teratogen. The second appears plausible if dioxin kills the embryo at the highest levels received by Ranch Hands and is a teratogen at intermediate levels. Either of these hypotheses were subject to elimination from consideration in the interpretations if it was contradicted by the data. For example, the first would be dropped from consideration and the second would be supported if the number conceptions were highest at intermediate dioxin levels. Conversely, the second would be dropped and the first supported if the number of conceptions increased with dioxin.

12.4 The Baseline Analysis

In the baseline AFHS report, the significance of the association between the father's group (Ranch Hand, Comparison) and the mothers report of any post-SEA birth defect was assessed with adjustment for reported pre-SEA defects. The analysis found significant variation in relative risk with time of birth relative to SEA. The Ranch Hand rate of reported pre-SEA defects was less than the Comparison rate and the Ranch Hand rate of reported post-SEA defects was greater than the Comparison rate. A repetition of this analysis with medical record verification replacing the mother's report found a similar significant variation in relative risk with time of birth relative to SEA.

Because the databases have been subjected to continual quality control since baseline, the baseline analysis was repeated, again using the mother's report. This repetition also revealed significant variation in relative risk with time of birth relative to SEA. Among pre-SEA children the rate of reported defects in Ranch Hand children (58.8 per 1000) was less than the Comparison rate (76.7 per 1000), but among post-SEA children the Ranch Hand rate (128.0 per 1000) was greater than the Comparison rate (86.2 per 1000).

The baseline finding motivated the verification of conception outcomes and birth defects which are the subject of this report. In the interim, advances in chemistry allowed the direct measurement of dioxin in human serum possible. Since 1987, 932 Ranch Hands and 1202 Comparisons have received the serum dioxin assay, providing a more direct assessment of dioxin exposure than simply group membership.

12.5 Semen

The statistical significance of the association between the father's dioxin level and sperm count and the percentage of abnormal sperm was assessed based on the testing of semen specimens collected during the baseline examination in 1982.

We found no significant association between dioxin and sperm count, low sperm count rate or the percentage of abnormal sperm. We conclude that there is no association between dioxin and any of these variables.

12.6 Conceptions

These analyses addressed the significance of associations between dioxin and miscarriage, total adverse outcome and total conceptions. Total adverse outcome was defined as miscarriage, tubal pregnancy, other (non-induced) abortive pregnancies, or stillbirth.

A pre-post SEA Model 3 analysis without restriction to full siblings found a significant association between categorized dioxin and total conceptions, caused by increased post-SEA conceptions in Ranch Hands in the High category (mean=2.47) relative to Comparisons in the Background category (mean=2.17). Significant associations in Model 1 analyses in full siblings were due to increasing mean numbers of post-SEA conceptions with dioxin. Significant associations in Model 2 analyses between dioxin and total conceptions among full sibling children were due to increasing conceptions with dioxin in Ranch Hands with late tours, opposite to the corresponding decreasing pre-SEA trends. These findings do not support and sometimes contradict the hypothesis that high levels of dioxin kill the embryo. Thus, these data do not support the theory that high anomaly rates should occur at intermediate levels of dioxin (this is the second of the two considered dose-response patterns). The "expected dose-response pattern" therefore is the linear one in which the highest anomaly rate occurs at the highest levels of dioxin.

Analyses of post-SEA miscarriage, total adverse outcome and total conceptions, were predominently negative. An unadjusted Model 2 analysis found significant variation in the association between dioxin and miscarriage with time since tour in Ranch Hands with more than 10 ppt current dioxin. This finding was caused by a positive association in conceptions of Ranch Hands with late tours and a negative association in Ranch Hands with early tours. That dioxin should act adversely in one stratum of Ranch Hands and beneficially in another is difficult to conceptualize and, therefore, this finding appears unrelated to dioxin.

Adjusted analyses of post-SEA miscarriage were either negative or were complicated by significant interactions with covariates. There was no pattern common to the 16 interactions and most were not consistent with the expected dose-response pattern. For example, an adjusted Model 2 analysis found a significant interaction with the father's military occupation in SEA. Among officers, miscarriages decrease with dioxin and among enlisted personnel there were no consistent patterns. In some enlisted strata the highest miscarriage rate occurred in Ranch Hands having intermediate dioxin levels and in one stratum Ranch Hands with the lowest dioxin level have the highest rate. An adjusted Model 3 analysis found a significant interaction with the mother's age. In mothers aged 27 or younger, Ranch Hands in the High category had a higher miscarriage rate (175.4 per 1000) than Comparisons in the background category (126.0 per 1000), but among mothers older than 27 the rate in the High category (126.6 per 1000) was less than the rate in the Background category (147.1 per 1000). In summary, the post-SEA miscarriage findings were either nonsignificant or, if significant, were inconsistent with the expected dose-response pattern or were complicated by covariate interactions that revealed no patterns suggestive of a dioxin effect. These findings are therefore most likely not related to dioxin.

Post-SEA analyses of total adverse outcome were either negative or found significant associations caused by trends that lack coherent explanation or were complicated by interactions with covariates. For example adjusted Model 1 analyses found significant interactions with the mother's age in children of Ranch Hands with more than 10 ppt and with the father's race and military occupation. The interaction with the mother's age was due to a positive association with dioxin in mothers aged 27 or younger and no association in mothers older than 27. The interactions with race and military occupation were caused by a negative association in children of nonblack enlisted groundcrew, a positive association in children of Black enlisted groundcrew and no association in children of officers. These results were generally weak, inconsistent and were sometimes contradictory or opposite to the expected dose response pattern. They are therefore most likely not related to dioxin.

Post-SEA analyses of total conceptions were either negative, inconsistent, or found positive associations between total conceptions and dioxin. For example, an adjusted Model 2 analysis found a significant interaction effect with time since tour caused by a positive association in children of Ranch Hands with late tours and a negative association in children of Ranch

Hands with early tours, but neither of these were significant. Two unadjusted Model 3 analyses found significant results caused Ranch Hands in the High dioxin category having more conceptions than Comparisons in the Background category. These findings contradict the theory that high levels of dioxin kill the embryo and are not indicative of an adverse effect of dioxin on total conceptions.

In summary, we find no evidence that dioxin is adversely associated with miscarriage, total adverse outcome or total conceptions. The observed increases in total conceptions with dioxin contradict and therefore eliminate from consideration the theory that dioxin at high levels kills the embryo. Therefore, the "expected dose-response" was reduced to a single pattern: increasing anomalies with increasing paternal dioxin.

12.7 Birth Weight

Pre-post SEA analyses of birth weight were predominantly negative. The few significant findings were not suggestive of a dioxin effect. For example, a Model 1 analysis of birth weight found a significant interaction with time since tour caused by a decreasing birth weights in pre-SEA children and a increasing in birth weights in post-SEA children. This change was due to an increase mean birth weight from pre- to post-SEA in children of Ranch Hands with the highest dioxin levels. Because low birth weights were considered adverse, this finding is not interpretable as an adverse effect of dioxin. A similar significant interaction was found after restriction to full siblings. In a Model 3 analysis of low birth weight, a significant interaction was found with time of conception in the contrast of children of Ranch Hands in the Unknown category with children of Comparisons in the Background category. Among pre-SEA children, the rate of low birth weight in Ranch Hand children (61.2 per 1000) was less than that in children of Comparisons (73.5 per 1000) and in post-SEA children, the rate in Ranch Hand children (93.3 per 1000) was greater than that in children of Comparisons (41.9 per 1000), but this change was due more to the decrease in the Comparison rate than to the increase in the Ranch Hand rate, a pattern that cannot be attributed to dioxin. A similar finding was revealed after restriction to full sibling children.

Post-SEA analyses of birth weight were generally negative or were complicated by interactions with covariates that made no sense. For example, a Model 1 analysis of birth weight found significant interaction with the father's race and the mothers' smoking, due to a significant decrease in birth weight with dioxin in children of Black fathers whose mother did not smoke during pregnancy and a borderline significant weight reduction in children of nonblack fathers whose mother did smoke during pregnancy. After restriction to full siblings, significant interaction with only the mother's smoking was found. In that analysis, there was a significant reduction in birth weight with dioxin in children of mothers who smoked during pregnancy and no significant reduction in children of mothers who did not smoke during pregnancy. A Model 2 analysis of birth weight found a significant interaction with the father's race; birth weight decreased borderline significantly with dioxin in children of Black fathers who had early tours but there were no

significant associations in the other 3 strata. After restriction to full siblings, no significant interactions with covariates were found, but in that analysis, birth weight decreased with dioxin in children of fathers who had late tours and increased in children of father's who had early tours but neither of these associations was significant. A Model 3 analysis of birth weight found a significant interaction with the father's race; the birth weight of children born to Black Ranch Hands in the High category was significantly less than of children born to Black Comparisons in the Background category and a weaker reduction was found in children of nonblack Ranch Hands in the High category. After restriction to full siblings, children of Ranch Hands in the High category were found to have significantly lower birth weight than children of Comparisons in the Background category.

Post-SEA analyses of low birth weight were generally negative or were complicated by interactions with covariates. For example, a Model 1 analysis found a significant interaction with the father's race and with the mother's drinking during pregnancy. This interaction was due to a significant increase in the rate of low birth weight with dioxin in children of nonblack father's whose mothers drank during pregnancy, however, the number of children (35) and the number with low birth weight (3) in this stratum were small; no significant associations were found in the other 3 strata. After restriction to full siblings, significant interaction was found with the mother's smoking during pregnancy and with the time of conception. This interaction was caused by a significant reduction in the risk of low birth weight with dioxin in children conceived within 2 years of the father's departure from SEA whose mother did not smoke during pregnancy. A Model 2 analysis of low birth weight found a significant interaction with time of conception. This interaction was caused by a significant increase in risk with dioxin in children conceived more than 6.5 years after the father's departure from SEA whose father had an early tour (relative risk=1.84). In the same analysis, however, there was a borderline significant decrease in risk with dioxin in children conceived within 2 years of the father's departure from SEA whose father had an early tour (relative risk=0.40). After restriction to full siblings, no significant associations were found between low birth weight and dioxin. A Model 3 analysis of low birth weight found a significant interaction with the father's military occupation in SEA, caused by a significant increase in risk with dioxin in children of fathers who were enlisted ground personnel (relative risk=2.58). After restriction to full siblings, significant a interaction with the father's race and military occupation in SEA were found, caused by significant increases in risk with dioxin in children of Ranch Hands in the High category who nonblack enlisted flyers or who were nonblack enlisted ground personnel.

These findings are generally weak and inconsistent. That (1) the nature of the interaction changes after restriction to full siblings and (2) birth weight decreases with dioxin in some strata and increases in others and (3) many of the interactions are based on sparse data, suggest that these findings are chance occurrences. We find no evidence in these data that birth weight is adversely associated with the father's dioxin level.

12.8 Pre-post SEA Birth Defects

Analyses were carried out to determine whether the variation in association between paternal dioxin level and birth defects with time of conception relative to SEA was attributable to a specific category of defect. After comprehensive reanalysis by birth defect category, the finding could not be attributed to a specific type of defect. Additionally, adjustment for the father's dioxin level revealed no significant results. Hence, the group difference found out baseline remains after verification but is not significantly associated with dioxin and cannot be attributed to a particular category of anomaly.

Each category of anomaly was additionally assessed for post-SEA dioxin effects with adjustment for pre-SEA anomalies using Models 1, 2 and 3. Each analysis was carried out first on all children and then with restriction to full siblings. All of these pre-post-SEA were unadjusted for covariates.

The only significant results in these analyses were the Model 2 assessments of digestive system anomalies and musculoskeletal deformities in children of Ranch Hands having more than 10 ppt current dioxin. The digestive system findings were caused by increasing post-SEA rates in children of Ranch Hands with late tours and no trends in post-SEA rates in children of Ranch Hands with early tours. The musculoskeletal findings were caused by decreasing post-SEA rates in children of Ranch Hands with early tours, opposite to a corresponding increasing trend in pre-SEA rates. These findings are inconsistent with each other and lack credible biologic explanation and therefore appear unrelated to dioxin.

In summary, a repetition of the baseline analysis with verified birth defect data revealed a significant change in birth defect rates with the Ranch Hand rate being less than the Comparison rate among pre-SEA children and greater than the Comparison rate among post-SEA children. However, after accounting for paternal dioxin level, we found no evidence that this effect was confined to a specific birth defect category and we found no significant association between this change in risk and dioxin. We conclude that this change in relative risk is unrelated to dioxin.

12.9 Post-SEA Birth Defects

The significance of the association between dioxin and post-SEA birth defects was assessed within each of 13 birth defect categories in four separates series of 3 analyses based on Models 1, 2 and 3, without adjustment for pre-SEA reproductive experiences. Analyses were first carried out on all children and then with restriction to full siblings and each of these was done first without and then with adjustment for covariates.

Few significant associations were found. Those that were found did not appear consistently across related analyses and most were not suggestive of a plausible dioxin effect. For example, a significant association was found between initial dioxin and circulatory system and heart anomalies, but the rate (6.4 per 1000) among children of Ranch Hands having the highest initial dioxin levels was less than that among children of Ranch Hands at the lowest dioxin levels (28.3 per 1000). In a Model 3 analysis restricted to full sibling children, a significant association was found between categorized dioxin and circulatory system and heart anomalies, but this was due to a high rate (47.3 per 1000) among children of Ranch Hands in the Low category relative to children of Comparisons in the Background category (17.2 per 1000) and a low rate among children of Ranch Hands in the High category (0 per 1000). In a Model 2 analysis, a significant association was found between current dioxin and anomalies of the ear, face and neck, but this was caused by an increase in anomalies with dioxin among children of Ranch Hands having early tours and a decrease in anomalies among children of Ranch Hands having late tours. A significant association was found in a Model 3 analysis of genital anomalies, but the pattern was not consistent with the expected dose-response. The rate among children of Ranch Hands in the Low dioxin category (51.7 per 1000) was greater than that among children of Ranch Hands in the High category (13.2 per 1000).

Several adjusted analyses of post-SEA total congenital anomalies and musculoskeletal deformities were complicated by significant interaction with covariates. Examination of these did not reveal meaningful patterns. For example, Model 3 analyses of total congenital anomalies found a significant interaction with the father's military occupation in SEA. Among officers, children of Ranch Hands in the High dioxin category had a lower rate (0 per 1000) than children of Comparisons in the Background category (217.9 per 1000). Among children of flying enlisted and enlisted ground personnel, children of Ranch Hands in the Low dioxin category had higher rates (433.3 per 1000 and 317.3 per 1000) than children of Comparisons in the Background category (228.9 per 1000 and 212.7 per 1000) but the rates in children of Ranch Hands in the High category were not significantly elevated. A Model 3 analysis of musculoskeletal deformities also found a significant interaction with the father's military occupation in SEA. In a pattern similar to that of total congenital anomalies, children of Ranch Hand officers in the Low category had a low rate (0 per 1000) relative to children of Comparisons in the Background category (155.6 per 1000) and the rates in children of enlisted flyers and enlisted ground personnel were not significantly elevated with respect to the rate in corresponding children of Comparisons in the Background category. In summary, analyses of total congenital anomalies and musculoskeletal deformities found significant variation in relative risk, but no clear pattern emerged. This suggests that these results are chance occurrences and that there is no underlying association with dioxin.

In conclusion, there is no consistent evidence of an association between dioxin and birth defects among post-SEA children. These findings are weak, inconsistent and lack credible biologic interpretation. They therefore appear unrelated to dioxin.

12.10 Birth Defect Severity

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

Unadjusted pre-post SEA analyses were carried out with severity reduced to 2 categories (major, not major), first based on all children and then with restriction to full siblings using each of the 3 models.

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

Model 2 analyses of post-SEA severity in 3 categories found significant associations with dioxin in all children and in full siblings, but these findings were caused by the highest rate of major defect occurring in children of Ranch Hands having early tours and intermediate dioxin levels. Corresponding analyses of severity in 2 categories were negative. These findings appear inconsistent with the expected patterns and are not suggestive of a dioxin effect.

Without and with restriction to full siblings, 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. These findings were due to 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 variation in effect with the mother's smoking and the father's military occupation in SEA. However, within 2 of the 4 smoking by occupation strata the children of fathers in the High dioxin category had the lowest rate of major defects. Significant findings in 1 of these strata were caused by the rate of major defect in children of Ranch Hands in the Low dioxin category 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 some 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 therefore not suggestive of a dioxin effect. We conclude that there is no evidence in these data that dioxin is adversely associated with birth defect severity.

12.11 Selected Birth Defects

Twelve birth defects (anencephaly, spina bifida, hydrocephalus, cleft palate, cleft lip/palate, esophageal atresia, anorectal atresia, polydactyly, limb reduction deformities, hypospadias, congenital hip dislocation, Down's syndrome) and 4 developmental anomalies (disturbance of emotion, hyperkinetic syndrome of childhood, specific delays in development, mental retardation) were investigated. Of these, there were only enough occurrences of specific delays in development and hyperkinetic syndrome of childhood to permit statistical assessment of associations with dioxin.

Pre-post SEA analyses without adjustment for covariates were carried out with Models 1, 2 and 3, first on all children and then with restriction to full siblings. Post-SEA analyses using the same models were also carried out on all children and then with restriction to full siblings. Each of the post-SEA analyses was carried out without and then with adjustment for covariates.

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 hypothesis that dioxin is adversely associated with delays in development; the corresponding adjusted analyses were negative. The Model 1 findings were caused by a reversal in pre-SEA and post-SEA trends; the pre-SEA trends were increasing and the post-SEA trends were decreasing or not increasing 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 and are inconsistent with each other and are therefore 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 siblings. This finding was caused by a decreasing rate of hyperkinetic syndrome with dioxin in children of Ranch Hands. 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 was found in a Model 3 analysis of specific delays in development. This interaction was caused by a significantly elevated rate in children of Ranch Hands in the Low dioxin category older than 30 years of age with the time of conception less than or equal to 4 years since 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.

12.12 Multiple Birth Defects

Of 1772 post-SEA children included in these analyses, 57 had multiple defects that could not be attributed to syndromes. Model 1 and 2 analyses of these 57 multiple birth defects found no significant associations with dioxin. Model 3 analyses found increased rates of multiple birth defects in children of Ranch Hands in the Low category relative to children of Comparisons in the background category. However, the rates in children of Ranch Hands in the High category were not significantly elevated. These findings are weak and inconsistent with the expected dose-response. We conclude that there is no evidence in these data that dioxin is adversely associated with multiple birth defects.

12.13 Neonatal and Infant Mortality

Analyses of post-SEA infant death were either negative or could not be carried out due to insufficient data. Analyses of post-SEA neonatal death found significant associations in two Model 3 analyses. Both of these findings were caused by the rate of post-SEA neonatal death being higher in children of Ranch Hands in the High dioxin category than in children of Comparisons in the Background category. However, the corresponding pre-post SEA data show that pre-SEA children of Ranch Hands in the High category also had a higher rate then pre-SEA children in the Background category. Therefore, these finding appear attributable to chance rather than to dioxin.

These analyses were generally negative and the two significant associations found in analyses of neonatal death were chance occurrences. We conclude that there is no association between dioxin and infant or neonatal mortality.

12.14 Summary

This study was motivated by significant variation at baseline in the rates of birth defects reported by spouses and partners of study participants. The Ranch Hand rate was lower than the Comparison rate in children born prior to the father's military service in SEA and greater than the Comparison rate in children born after the father's service in SEA, a finding that some interpret as suggestive of an adverse effect of dioxin on reproductive outcome. However, its interpretation as a dioxin effect was subject to objection because (1) the analysis grouped all defects together rather than by category, (2) the analysis was based on reported rather than verified birth defects and (3) because no account was taken of individual paternal dioxin levels.

Verification of all live births and conceptions reveal that Ranch Hands and Comparisons over- and under-reported birth defects similarly. About 2% of pre-SEA and post-SEA children were over-reported by both Ranch Hands and Comparisons. Both groups under-reported 14% of post-SEA defects and about 7% of pre-SEA defects.

A repetition of the baseline analysis using verified data derived from doctor and hospital records showed that the original finding remained. Subsequent analyses within each of 13 CDC categories of anomaly were carried out. Analyses in all categories except total congenital and nervous system were negative. The association in the nervous system category was in the same direction as that of total congenital, but there were too few nervous system anomalies (9 in Ranch Hand children and 10 in Comparison children) to attribute the overall result to anomalies of the nervous system.

Pre-post analyses of anomalies in each of the 13 categories were carried out using Models 1, 2 and 3 to assess the association between changes in rates and dioxin. No consistent or plausible evidence was found in any category of birth defect relating dioxin to a pre-post SEA reversal in rates. Thus, the baseline finding is still present in these data, but it is not related to dioxin. Additionally, the finding cannot be fully ascribed to any category of anomaly.

The lack of significant association between dioxin and the number of conceptions and between dioxin and any considered semen characteristic suggests that Ranch Hand dioxin exposure is unrelated to their ability to father children. The lack of consistent associations between dioxin and miscarriage, total adverse outcome, birth weight, any of 13 categories of birth defects and neonatal death suggests that dioxin is unrelated to reproductive outcomes fathered by this exposed population.

This study was based on reproductive outcome data verified from medical records up to the age of 18. In contrast, the CDC study [15] is based on data derived from parental report and birth records. Hence, some of our birth defect rates were higher than those reported by the CDC. For example, the crude rate of total congenital anomalies in post-SEA Comparison children is 266.9 per 1000 and the rate in Army Vietnam veterans derived from parental report is 64.6 per 1000. The two studies are comparable with regard to rates of specific defects based on verified data. For example, the rate of nervous system anomalies in post-SEA Comparison children is 1.5 per 1000 and the corresponding rate in post-SEA children of Army Vietnam veterans is 2.6 per 1000. The miscarriage rates in the two studies are similar. The miscarriage rate among post-SEA conceptions of Ranch Hands and Comparisons included in these exposure analyses is 145.5 per 1000; the miscarriage rate in post-SEA conceptions of Army veterans is 104 per 1000.

This and the CDC studies are generally negative. However, the CDC study found an association between service in Vietnam and nervous system anomalies; all analyses of nervous system anomalies except a pre-post SEA finding which was unadjusted for dioxin level, were negative in this study.

In any epidemiologic study, the possibility that bias in design or conduct may have affected the results need to be considered. It is unlikely that these results are biased due to differential reporting because the existence and contents of birth certificates, newborn clinic records or death certificates cannot be influenced by the parents. Additionally, these data were collected and verified at a time when the fathers had not yet received their dioxin results. However, we were concerned that Ranch Hand parents may have actively sought medical opinion regarding birth defects in their children, making birth defects more verifiable in their children than in Comparison children. We found no evidence of this 'verification' bias. We also investigated selection bias for the dioxin assay and found that children of enlisted ground personnel who volunteered for the assay were more likely to have birth defects than children of enlisted ground personnel who were not assayed. This selection bias is not detrimental to this report, however, because the birth defect rate was higher in children of assayed fathers than in children of unassayed fathers.

The many endpoints and multiple analyses in this report increase the likelihood that significant results will be found. In fact, if there is no relationship between dioxin and reproductive outcome, about 5% of the tests should be expected to produce significant results (p-values less than 0.05). The occurrence of significant results when there is no true effect is called the multiple testing artifact and is common to all large studies. There is no statistical procedure than can distinguish between artifactual results and those which are due to a true effect. Instead, we have relied on consistency and strength of association to interpret these findings. Based on these criteria we have concluded that all of the findings in this report are artifactual.

The few positive associations found between dioxin and the reproductive outcomes study in this report were generally weak, inconsistent or biologically implausible. These data provide no support for the theory that dioxin is adversely associated with reproductive outcome.

Whether dioxin exposure of the mother before or during pregnancy results in abnormalities in the developing fetus or child could not be addressed in this study and remains an open question.

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