Testimony of

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Chairman Simpson and Members of the Committee, thank you for this opportunity to discuss the mistaken assignment of a suggestive link between Agent Orange exposure of fathers and the appearance of spina bifida in their children. I will discuss three points: first will be a description of the Air Force's Ranch Hand Study,[1] second, a discussion of the process by which the Institute of Medicine[2] reached its conclusion about Agent Orange and spina bifida, and third is an analysis that demonstrates that the IOM conclusion is incorrect.

IOM considered evidence about possible links between Agent Orange exposure of fathers and birth defects in both its 1993[3] and its 1996 reports. In 1993, it suggested no link, and, as we all know, in 1996, it concluded that there was "limited/suggestive evidence for an association between exposure to herbicides used in Vietnam and spina bifida in offspring" (IOM 1996 at p. 1-8). The reason for the changed conclusion was information in the Ranch Hand study (IOM 1996 at p. 9-8).

Before discussing the Ranch Hand study, I will point out that there is no known biological mechanism by which parental exposure to Agent Orange can cause birth defects.[4] Neither 2,4-D nor 2,4,5-T, the two herbicides that were the principle

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[1] Wolfe, W.H., J.E. Michalek, J.C. Miner, *et al.* 1995. *Epidemiology* 6:17-22.
[2] Institute of Medicine. 1996. *Veterans and Agent Orange: Update 1996.* National Academy Press: Washington, DC.
[3] Institute of Medicine. 1993. *Veterans and Agent Orange.* National Academy Press: Washington, DC.
[4] Institute of Medicine. 1993. At pp. 593-595.

components of Agent Orange,[5] nor dioxin[6] is a mutagen, and none can affect the DNA in a sperm cell. Both 2,4-D and 2,4,5-T are eliminated from the body in a period of weeks, so that those chemicals would not have been present in the fathers' bodies when children were conceived after Vietnam service. Dioxin, on the other hand, is very persistent in the body, and it is present in all of us. Since dioxin cannot affect DNA, the only method by which dioxin in the father could cause birth defects is by being transferred to the mother through semen. The few molecules of dioxin that would be transferred would be added to the trillions more molecules in the mother's body. How could that tiny addition have an effect? It could not.

The Air Force study compared birth outcomes of the children born to Ranch Hands, men with known exposures to herbicides, to the outcomes for children born to a Comparison group that had no herbicide exposure. There was no *a priori* reason to think that Agent Orange was associated with any particular birth defects, and the Air Force scientists cast a wide net. They compared total birth defects in the children of Ranch Hands and Comparisons, and they compared the occurrence and frequency of every single birth defect identified in the children of Ranch Hands, Comparisons, or both.

What would we expect if exposures to herbicides had absolutely no impact on birth defects? Would we expect exactly the same kinds of birth defects in both exposed and unexposed populations? Or exactly the same numbers? Of course not, based on chance, we would expect that some birth defects would be more common in the exposed group and that some would be more common in the non-exposed group, but that birth defects would be about equal among the children of Comparisons and Ranch Hands.

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[5] Mortelmans, K., S. Haworth, W. Speck, *et al.* 1984. *Toxicology and Applied Pharmacology 75*:137-146.

[6] Environmental Protection Agency. 1994. *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds.* USEPA: Washington, DC. [EPA/600/BP-92-001a.] Volume I of III at pp. 6-12 to 6-14.

In contrast, what would we expect if exposure to herbicides increased birth defects? If, by some completely unknown mechanism, the herbicides increased the frequency of all birth defects, we would expect significantly more birth defects among the Ranch Hand children. If it caused an increase in the frequency of a particular birth defect, we would expect that birth defect to be significantly more common in the Ranch Hand children.

There is no statistically significant difference between the frequency of birth defects in the Comparison and Ranch Hand populations. The ratio of birth defects/child was 0.21 in the Comparisons and 0.22 in the Ranch Hands. When comparisons were made of the frequency of birth defects in different organ systems, birth defects in four organ systems were more common in the children of the Comparisons, and birth defects in the other six organ systems were more common in the children of the Ranch Hands. None of the differences was statistically significant. This distribution of birth defects is what we would expect if exposures to herbicides have no impact on birth defects.

Two specific anomalies and two developmental disabilities were common enough for statistical analysis on the bases of the fathers' herbicide exposures. The frequencies of the two specific anomalies--major birth defects and multiple birth defects--were comparable in the children of the Comparisons and Ranch Hands.

To examine the possible effect of increasing herbicide exposures, the Ranch Hands were divided into three groups--(1) those with no evidence of exposure above background levels, (2) those with low exposures, and (3) those with high exposures. If herbicides cause birth defects, we would expect the frequency of the birth defects to increase along with exposures. That is not what was found. Instead, major birth defects and multiple birth defects were most common in the children of Ranch Hands with low exposures. There is no way to explain those results as being related to herbicide exposures. If increasing exposures caused those birth defects, the defects would be more common in the children of the "high" exposure group of Ranch Hands. The most reasonable explanation

is that herbicides had no effect and that the distribution of birth defects in children of men with background, low, and high exposures was a matter of chance.

Similarly, examination of the two developmental disabilities that were sufficiently common for statistical analysis supports the conclusion that there is no relationship between herbicide exposures and frequency of birth defects.[7] Hyperkinetic syndrome was most common in the children of the background exposure group. Delayed development was more common in the children of the background exposure group than in those of the high exposure group.

Rather than dwelling on the small differences in the frequency of these anomalies and developmental disabilities in the children of men with different exposure histories, it makes more sense to say that there is no relationship between exposure and these anomalies and disabilities. Indeed, that is how IOM interpreted those data.

The Ranch Hand study reported the numbers of 14 specific anomalies or developmental disabilities identified in the children of Comparisons or Ranch Hands or both for which "Counts and rates...[were] too sparse to analyze..." (Wolfe *et al.* 1995, p. 20).

Two neural tube anomalies--one case of anencephaly and three cases of spina bifida--occurred only in the children of Ranch Hands. In addition, two other birth defects--one case of polydactyly and one case of reduced limb deformity--occurred only in the Ranch Hands' children.

In the past, cleft palate and cleft lip/palate had often been suggested as possibly associated with dioxin because exposure of pregnant mice to dioxin increased the

[7] There were 71 cases of delayed development in the children of both the Comparisons and Ranch Hands and 32 cases of hyperkinetic syndrome in the children of Comparisons and 30 cases in the children of Ranch Hands.

frequency of cleft palate in their offspring.[8] There is, however, no evidence that exposure of male breeding mice to Agent Orange causes any effect on their offspring.[9] Interestingly, cleft palate and cleft lip/palate occurred only in the Comparison children in the Ranch Hand study. In addition to cleft palates that occurred only in Comparisons' children, the single case of hydrocephalus that was seen in the study occurred in the child of a Comparison.

Given the distribution of birth defects between Comparisons and Ranch Hands, there is as much logic in suggesting that exposures to herbicides protects against cleft palate and hydrocephalus as there was in IOM's concluding that the results about spina bifida are suggestive of an association.

Neither the authors of the Ranch Hand study, the Department of Health and Human Services committee that reviewed the study before its publication,[10] the reviewers and editors of the journal *Epidemiology* that published the Air Force study, or a scientist who commented on the Air Force study for *Epidemiology*[11] concluded that the distribution and frequency of birth defects offered any evidence for a connection between herbicide exposure and birth defects.

Why did IOM reach its conclusion that the evidence was "limited/suggestive"? IOM assigns that classification when

> Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent.[12]

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[8] Courtney, K.D. and J.A. Moore. 1971. *Toxicology and Applied Pharmacology 20:*396-403.

[9] Lamb, J.C., J.A Moore, and T.A. Marks. 1980. *Evaluation of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxicity in C57BL-6 mice: Reproduction and fertility in treated male mice and evaluation of congenital malformations in their offspring.* National Toxicology Program: Research Triangle Park, NC. [NTP-80-44].

[10] I chaired that committee when it reviewed the Air Force birth defects study.

[11] Lindbohm, M-L. 1995. *Epidemiology 6:*4-6.

[12] Institute of Medicine. 1993. At p. 6.

IOM downplayed the role of chance and confounders in its evaluation. Certainly chance can explain the spina bifida cases among the children of Ranch Hands, just as it can explain the absence of children with cleft palates in the same population.

"Confounders," which are factors that might contribute to an apparent association between an exposure and an effect, must always be considered in serious epidemiology. Is there some other factor that could be associated with spina bifida in the Ranch Hand study? Although we do not know the causes of or methods to prevent most birth defects, there is convincing evidence that too-low levels of the vitamin folic acid in the diets of pregnant women increases the risk of babies with spina bifida and anencephaly. In fact, the Centers for Disease Control's Division of Birth Defects and Developmental estimates that 60 percent of those birth defects can be prevented by adequate amounts of folic acid in the diets of women.[13] Could this confounder as well as chance be involved in the distribution of the spina bifida cases in the Ranch Hand study? Of course. I think that the IOM paid too little attention to chance and confounding in its analysis.

The second part of IOM's criterion is more of a problem. Its focus on results from "one high-quality study" flies in the face of objective science that requires that all the data be considered and weighed together. In fact, it literally throws out any consideration of data that does not support an association because it lets the analysts focus on a single, isolated finding as the proof of their case. Associations can arise by chance or because of bias or confounding in the best of studies, and this criterion places undue weight on them. This criterion is bad science. It was not, as is sometimes suggested, forced on IOM by Congress. IOM set its own criteria.

IOM does not seriously consider the evidence that argues against any connection between herbicide exposures and birth defects. It does not wrestle with the problem that there is no biological model for how such effects could take place. It dismisses animal

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[13] Oakley, G.P., Jr. 1993. *Journal of the American Medical Association 269:*1292-1293.

tests that support the idea that such effects do not occur. IOM states (IOM 1996 p. 9-18) that "Laboratory studies of the potential developmental toxicity...of TCDD as a result of exposure to adult male animals are too limited to permit conclusions." This summation ignores the study by Lamb *et al.* that showed that feeding Agent Orange to male mice caused no birth defects even when it caused toxic effects in the male mice.

The IOM also brushed aside the study of 15,291 births to residents of Seveso, Italy. Seveso was the scene of a chemical plant accident in 1976 that spread dioxin and other chemicals over an area with a population of 37,000. In 1988, a group of Italian physicians published a paper that compared the frequency and kinds of birth defects in children born in the Seveso area in the six years after the accident to those in children born in the surrounding, uncontaminated area during the same period.[14]

Information from Seveso contradicts the IOM interpretation of the Air Force study. The Air Force reported five nervous system anomalies in the Ranch Hand children and three in the Comparison children. If there is a relationship between dioxin exposure and nervous system anomalies, those birth defects would be expected to be higher in the children born to the exposed parents at Seveso. There were 2 such defects among the 2900 children born to the exposed parents and 22 in the 12391 children born to the unexposed parents. The frequency of such birth defects is 0.07 percent in the exposed group and 0.17 percent in the unexposed group,[15] or 2.5-times higher in the unexposed group. The Seveso data provide no support for the idea that dioxin exposure causes central nervous system defects.

Some dioxin exposures were higher at Seveso than those experienced by the Ranch Hands (see table 1), more people were exposed at Seveso, and, very importantly, both men and women were exposed. Table 2 presents the results of calculating the

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[14] Mastroiacovo, P., A. Spagnolo, M. Ernesto, *et al.* 1988. *Journal of the American Medical Association 259:*1668-1672.

[15] I included "neural tube defect," "microencephaly," and "other CNS defects" from Mastroiacovo *et al.* in this tabulation.

expected number of cases of spina bifida in the Seveso population assuming that IOM's conclusion about the relationship between dioxin and spina bifida is correct. The absence of spina bifida from the residents of the contaminated areas of Seveso (Zones A, B, and R) contradicts IOM's conclusion. More generally, the failure of the high exposures to both men and women at Seveso to increase the frequency of any or all birth defects argues that dioxin has not caused human birth defects.

Conclusion

No biological mechanism is known that would explain how dioxin exposure of men could cause birth defects in their children. In support of that statement, an animal experiment demonstrated that exposing male mice to herbicides did not increase birth defects among their offspring. None of the other epidemiologic studies that IOM cites as supporting its conclusions about a "limited/suggestive" association between dioxin and spina bifida has any verifiable information about exposure.[16] The Ranch Hand study is best interpreted as showing no connection between paternal dioxin exposure and birth defects. The absence of spina bifida from the Seveso population with higher exposures and many more births than in the Ranch Hand study directly contradicts IOM's conclusion.

Congress asked IOM for a scientific evaluation. The IOM committee did not behave as scientists; it attached too much significance to a single finding, ignored conflicting evidence, and produced an incorrect evaluation. I believe that it is wrong and unfair to base policy on flawed science.

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[16] Centers for Disease Control. 1988. *Journal of the American Medical Association 260:*1249-1254.

Table 1

Dioxin Levels in the Ranch Hands and the Seveso Population

Ranch Hands, calculated initial dioxin concentrations.[b]

	Parental concentrationS (ppt)			
Classification	N[a]	mean	75%tile	maximum
background	283	---	---	<10
low exposure	241	60	---	109
high exposure	268	294	---	2020

Seveso population, measured concentrations in samples taken soon after exposure

	Parental Concentrations (ppt)			
Classification	N[a]	mean	75%tile	maximum
Zone A	198[c]	ca. 500[d]	ca. 2000[d]	56,000[e]
Zone B	435[f]	ca. 125[d]	---	---
Zone R	2439[f]	ca. 60[g]	---	---

a. Number of children born to parents in the indicated classification.

b. Joel Michalek, principal investigator, Air Force Ranch Hand study, email Aug. 28, 1996.

c. Number of births through December 1994 reported in Mocarelli, P., P. Brambilla, P.M. Gerthoux, *et al.* 1996. *The Lancet 348:* No birth defects have been reported among the children born to parents who lived in Zone A, although there was an excess of female births during the first seven years after exposure. In contrast, less than 50 percent of the children born to Ranch Hands were female (Joel Michalek, email, September 10, 1996), in line with the usual ratio of 106 male births to 100 female births.

d. Approximations supplied by Larry Needham, Centers for Disease Control, telephone conversation, Sept. 9, 1996.

e. Mocarelli, P., D.G. Patterson, A. Marocchi, and L.L. Needham. 1990. *Chemosphere 20:*967-974.

f. Mastroiacovo, P., A. Spagnolo, M. Ernesto, *et al.* 1988. *Journal of the American Medical Association 259:*1668-1672.

g. There are no published values for dioxin concentrations in residents of Zone R. I have approximated the concentration at 1/2 the Zone B concentration because: The dioxin level in the soil of Zone R is 1/3 the level in Zone B and animal mortality and the prevalence of chloracne (a skin disease that is indicative of dioxin exposure) are essentially the same in Zones B and R (Mastroiacovo *et al.* 1988. *Journal of the American Medical Association 259:*1668-1672.)

Table 2
Expected Numbers of Cases of Spina Bifida at Seveso If the
IOM's Conclusion is Correct Compared to the Reported Numbers

Area at Seveso	Calculated Number of spina bifida cases[a]	Observed Number of spina bifida cases[b]
Zone A	2.4 to 6.5	0
Zone A (75%tile)[c]	>2.4 to >6.5	0
Zone B	1.3 to 3.6	0
Zone R	3.5 to 9.7	0

a. 1 of 241 children fathered by Ranch Hands with low exposures (60 ppt dioxin) had spina bifida, and 2 of 268 children fathered by Ranch Hands with high exposures (294 ppt dioxin) had spina bifida. The expected frequency of cases of spina bifida in the Seveso children based on those relationships are calculated as:

$$\frac{\text{frequency spina bifida}_{RH}}{\text{dioxin concentration}_{RH}} = \frac{\text{predicted frequency spina bifida}_{S}}{\text{dioxin concentration}_{S}}$$

For instance, the frequency of spina bifida in the low exposure Ranch Hands is 1/241=0.4%, and their dioxin concentration is 60 ppt. The dioxin concentration of residents of Zone A is 500 ppt, and the relationship becomes

$$\frac{0.4\% \text{ spina bifida}}{60 \text{ ppt}} = \frac{X\% \text{ spina bifida}}{500 \text{ ppt}}, \text{ and } X = 3.3\%.$$

For the high exposure Ranch Hands the relationship is

$$\frac{0.7\% \text{ spina bifida}}{294 \text{ ppt}} = \frac{X\% \text{ spina bifida}}{500 \text{ ppt}}, \text{ and } X = 1.2\%.$$

Multiplying a frequency times the number of births yields an estimate of the expected number of births with spina bifida. For instance 198 births in Zone A multiplied times the expected frequency of 3.3% is 6.5, and multiplied by the expected frequency of 1.2% is 2.4.

b. No birth defect was reported in Zone A. One neural tube defect was reported in Zone B; from other information in Mastroiacovo *et al.* (1988), it appears that that birth defect was a brain tumor. One neural tube defect was reported in Zone R, and it is impossible to tell from the paper if that defect was a spina bifida. At my request, a scientist at the Centers for Disease Control contacted Dr. Mastroiacovo and asked him if any of the neural tube defects at Seveso was spina bifida. The scientist emailed on September 16, "I e-mailed Dr. Mastroiacovo but unfortunately all the records are in storage and he is leaving today for a meeting. I'm sure he would be happy to try to get the information for you at a later time, but he won't be able to access them before the hearing." (I'm surprised that this important information is not readily available.) However, an Italian scientist visiting Dr. L. Needham at CDC stated that there was no spina bifida in zones A, B, or R (telephone conversation, September 16, 1996).

c. The 75th percentile measurement in Zone A is about 2000. These calculations were based on an assumed average exposure of 2000 ppt, which is too low, and the assumption that the 25 percent of people with high exposures were parents of 25 percent of the children in Zone A.