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## FLASH UPDATE

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Wednesday, March 28, 2012

### [Does Paternal Exposure to Agent Orange Cause Birth Defects?](#)

#### COMMENTARY

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Received 29 December 2008; Accepted 5 February 2009

During the Vietnam war, large amounts of the herbicide Agent Orange were sprayed over the Vietnam countryside. Agent Orange consisted of the butyl esters of the herbicides 2,4-D and 2,4,5,-T, and was contaminated with the dioxin 2,3,7,8-TCDD, the most toxic dioxin congener in animals. Non-Vietnamese army personnel, Vietnamese army personnel, and Vietnamese civilians in the sprayed areas were exposed. The US studies involved the personnel of Operation Ranch Hand, who transported, loaded, and sprayed Agent Orange.

Concerns have repeatedly been raised about the long-term adverse health effects of this exposure, including the possibility of an increase in birth defects in the children of exposed men. Many studies have been done, with conflicting results.

A recent meta-analysis [Ngo et al., 2006] has claimed that there is indeed a significant increase of birth defects in children of exposed males, with an odds ratio of 1.95. (In fact, several of the studies used in the meta-analysis also included exposed females.) Schecter and Constable [2006] have drawn attention to some of the inadequacies of this study. In particular, the analysis includes many, mostly Vietnamese, studies that are unpublished, or inaccessible for review.

Inspection of the data presented in Ngo et al.'s article reveals other problems, which cast doubt on the validity of Ngo et al.'s meta-analysis. On inspection of the data (Fig. 1) one notes that: Vietnamese civilians and Vietnamese veterans tend to have higher odds ratios than non-Vietnamese veterans. Studies of Vietnamese civilians and Vietnamese veterans tend to have larger confidence intervals than those of non-Vietnamese veterans. Most of the Vietnamese studies are unpublished or inaccessible. This could be interpreted to mean that either: The Vietnamese populations were more heavily exposed than the non-Vietnamese veterans, and Agent Orange does cause birth defects in offspring of exposed persons at the concentrations to which the Vietnamese populations were exposed, but not at the exposures experienced by the Ranch Hand personnel, or: the Vietnamese studies are biased, and the Ngo meta-analysis does not provide evidence for an association of Agent Orange and birth defects. There is ample room for bias in this kind of study but, since most of the Vietnamese studies remain unpublished, or at least inaccessible, there is no opportunity to evaluate how rigorously they attempted to avoid such biases. There are, however, some indications that the studies may not be reliable.

Table 3 of Ngo et al. [2006] lists the frequency (in %) of malformed children in the unexposed comparison groups for each study. The frequencies range from 0.10% to 44%. Obviously, something is wrong! Ngo et al. acknowledge that there was under-ascertainment of malformed children, and that this could be differential, affecting unexposed more than exposed parents. In some studies, under-ascertainment must have been virtually complete in the unexposed group, reducing the frequency from the usual rate of about 30–50 per thousand (or higher if minor anomalies are included) to 1–5 per thousand. Thus most, if not all, of the elevated odds ratios appear to have resulted from a decrease in the comparison group rates, rather than an increase in the exposed rates. The results of such studies cannot be accepted with any confidence.

Finally, the (unpublished) article that states a 44% frequency in the unexposed group (Hung) is entitled “Spina Bifida investigated by Spinal X-ray among children of veterans exposed to defoliant in the war,” suggesting that spina bifida occulta was, contrary to general practice, being counted as a birth defect. These have a frequency of around 45% in the general population [Miller et al., 1962], which would account for Hung’s extraordinary result.

In conclusion, even though the unpublished articles included in the meta-analysis of Ngo et al., [2006] cannot be reviewed, the data \*Correspondence to: F. Clarke Fraser, OC, Ph.D., M.D., FRSC, 81 Chute Road, Bear River, NS, Canada B0S 1B0. E-mail: [f Fraser@auracom.com](mailto:f Fraser@auracom.com)

Published online 30 March 2009 in Wiley InterScience

([www.interscience.wiley.com](http://www.interscience.wiley.com))

DOI 10.1002/ajmg.a.32798

How to Cite this Article: Fraser FC. 2009. Does paternal exposure to Agent Orange cause birth defects?

Am J Med Genet Part A 149A:835–836. 2009 Wiley-Liss, Inc. 835 provided in the meta-analysis present problems that render their conclusion that “exposure to Agent Orange is associated with a statistically significant increase in risk of birth defects unacceptable.

#### ACKNOWLEDGMENTS

I thank Dr. David Erickson for his critical reading of this manuscript.

The fact that I am a consultant for Dow and Monsanto has had no influence on the content of this article.

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FIG. 1. Represents the Forest plot presented by Ngo et al. rearranged by exposed population. VNC, sprayed Vietnamese civilians; VNV, Vietnamese veterans; AU/US, Australian and US exposed veterans. The unpublished or inaccessible studies are designated by “U.”