

- comparison with unexposed controls. In: Proceedings of the second International Conference of Agent Orange/dioxin, Hanoi, Vietnam, 1994, pp. 188–99.
- ³⁹ 10/80 Committee, Hatfield Consultant Ltd. Retrospective Epidemiological Survey in four Communes - Aso, Huong Lam, Hong Thuong and Hong Van. In: 10-80 Committee and Hatfield Consultant Ltd (ed.). *Study of Impact and Development of Mitigation Strategies Related to the Use of Agent Orange Herbicides in the A Luoi Valley—Thua Thien Hue Province*. Hanoi: 10-80 Committee, 2000, pp. 161–210.
- ⁴⁰ Hung TM, Cuc PTK, Cau HD. Spina Bifida investigated by Spinal X-Ray among children of veterans exposed to defoliant in the war. In: 10-80 Committee (ed.). *Consequences of Chemicals Used in Vietnam War 1961–1971*. Hanoi: 10-80 Committee, 2000, pp. 50–59.
- ⁴¹ Schecter AJ, Constable JD. Elevated level of 2,3,7,8-Tetrachlorodibenzodioxin in adipose tissue of certain U.S. veterans of the Vietnam war. *Chemosphere* 1987;**16**:1997–2002.
- ⁴² Centers for Disease Control. Serum 2,3,7,8-Tetrachlorodibenzo-p-dioxin Levels in US Army Vietnam-are veterans. *JAMA* 1988;**260**:1249–54.
- ⁴³ Kang HK, Watanabe KK, Breen J *et al.* Dioxins and dibenzofurans in adipose tissue of US Vietnam veterans and controls. *Am J Public Health* 1991;**81**:344–49.
- ⁴⁴ Schecter AJ, Dai LC, Thuy LT *et al.* Agent Orange and the Vietnamese: the persistence of elevated dioxin levels in human tissues. *Am J Public Health* 1995;**85**:516–22.
- ⁴⁵ Schecter AJ, McGee H, Stanley JS, Boggess K, Brandt-Rauf P. Dioxins and dioxin-like chemicals in blood and semen of American Vietnam veterans from the state of Michigan. *Am J Ind Med* 1996;**30**:647–54.
- ⁴⁶ Michalek JE, Rahe AJ, Kulkarni PM, Tripathi RC. Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 1,302 unexposed Air Force Vietnam-era veterans. *J Expo Anal Environ Epidemiol* 1998;**8**:59–64.
- ⁴⁷ Schecter AJ, Dai LC, Papke O *et al.* Recent dioxin contamination from Agent Orange in residents of a southern Vietnam city. *J Occup Environ Med* 2001;**43**:435–43.
- ⁴⁸ Kang HK, Dalager NA, Needham LL *et al.* US Army Chemical Corps Vietnam veterans health study: preliminary results. *Chemosphere* 2001;**43**:943–49.
- ⁴⁹ Schecter AJ, Pavuk M, Constable JD, Dai LC, Papke O. A follow-up: high level of dioxin contamination in Vietnamese from Agent Orange, three decades after the end of spraying. *J Occup Environ Med* 2002;**44**:218–20.
- ⁵⁰ Kahn PC, Gochfeld M, Nygren M, Hansson M *et al.* Dioxins and dibenzofurans in blood and adipose tissue of Agent Orange-exposed Vietnam veterans and matched controls. *JAMA* 1988;**259**:1661–67.
- ⁵¹ Schardein JL. Principles of teratogenesis applicable to human exposure to drugs and chemicals. In: DiCarlo FJ, Oehme FW (ed.). *Chemically Induced Birth Defects*. New York: Marcel Dekker, Inc., 1985, pp. 1–48.
- ⁵² Institute of Medicine. Exposure assessment. In: Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, Institute of Medicine (ed.). *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam*. Washington DC: National Academy Press, 1998, pp. 135–268.
- ⁵³ Watanabe KK, Kang HK. Mortality patterns among Vietnam veterans: A 24-year retrospective analysis. *J Occup Environ Med* 1996;**38**:272–82.
- ⁵⁴ Dalager NA, Kang HK. Mortality among Army Chemical Corps Vietnam veterans. *Am J Ind Med* 1997;**31**:719–26.
- ⁵⁵ Centers for Disease Control. Post-service mortality among Vietnam veterans. The Centers for Disease Control Vietnam Experience Study. *JAMA* 1987;**257**:790–95.
- ⁵⁶ Boehmer TK, Flanders WD, McGeehin MA, Boyle C, Barrett DH. Post-service mortality in Vietnam veterans, 30-year follow up. *Arch Intern Med* 2004;**164**:1908–16.
- ⁵⁷ Edmonds LD, James LM. Temporal trends in the birth prevalence of selected congenital malformations in the Birth Defects Monitoring Program/Commission on Professional and Hospital Activities, 1979–1989. *Teratology* 1993;**48**:647–49.
- ⁵⁸ Nessel CS, Gallo MA. Dioxins and related compounds. In: Lippmann M (ed.). *Environmental Toxicants*. New York: Van Nostrand Reinhold, 1992.
- ⁵⁹ DeVito MJ, Birnbaum LS. Dioxins: model chemicals for assessing receptor-mediated toxicity. *Toxicology* 1995;**102**:115–23.
- ⁶⁰ Bryant PL, Reid LM, Schmid JE, Buckalew AR, Abbott BD. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on fetal mouse urinary tract epithelium in vitro. *Toxicology* 2001;**162**:23–34.
- ⁶¹ Couture LA, Harris MW. Characterization of the peak period of sensitivity for the induction of hydronephrosis in C57BL/6N mice following exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fundam Appl Toxicol* 1990;**15**:142–50.
- ⁶² Theobald HM, Peterson RE. Developmental and reproductive toxicity of dioxins and other ah receptor agonists. In: Schecter A (ed.). *Dioxin and Health*. New York and London: Plenum Press, 1994, pp. 319–32.
- ⁶³ Giri AK. Mutagenic and genotoxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin, a review. *Mutat Res* 1986;**168**:241–48.

Commentary: Agent Orange and birth defects in Vietnam

Arnold Schecter^{1*} and John D Constable²

The subject of Ngo *et al.*'s review¹ has been in the news since the 1960s: has exposure to Agent Orange sprayed in Vietnam between 1962

and 1971, or its dioxin contaminant 2,3,7,8-tetrachlorodibenzodioxin (or TCDD), resulted in an increased incidence of congenital malformations in Vietnam? Since 1983 there have been a number of Vietnamese conference presentations, which support the belief that Agent Orange exposure is linked to birth defects in Vietnam.^{2,3} However committee Reports of the US Institute of Medicine of the National Academy of Sciences, published as biennial reviews since

¹ University of Texas School of Public Health, Dallas Campus, Dallas, TX, USA.

² Harvard Medical School, Boston, MA, USA.

* Corresponding author. E-mail: Arnold.Schecter@UTSouthwestern.edu

1994, the most recent of which is 'Veterans and Agent Orange, Update 2004',⁴ conclude that, with the exception of spina bifida and anencephaly, the published peer-reviewed literature does not convincingly support an association between herbicide or dioxin exposure and birth defects in humans.

At a March 2005 Agent Orange meeting held under the auspices of The French–Vietnam Friendship Society in Paris the Final Manifesto of the Congress concluded that some of the Vietnamese population in the South had been exposed to dioxin, which presents a risk of severe medical effects but without specific effects being satisfactorily proven. The toxicological literature, on the other hand, shows fetal damage, including hydronephrosis, cleft palate, changes in hormonal development, and nervous system changes as a result of maternal exposure to dioxin in rodents.^{5,6}

In an admirable attempt to determine whether Vietnamese research over the last decades might shed a brighter light on this question, the authors reviewed many published and unpublished papers including abstracts, submitted or presented at meetings, and posters. Very little of this material, which they then used for their meta-analysis, has undergone any significant peer review. These papers include all the Vietnamese reproductive studies presented in 1983 at the International Herbicide conference held in Ho Chi Minh City in 1983.² The material was subsequently published, with extensive editorial comment and some revision, so as to make the information available to the scientific world.⁷ It is critical to point out that Western scientists in attendance were joined unanimously by their Vietnamese colleagues at the conference in concluding that, although several of these papers were suggestive, or even very suggestive, none of them proved, to international standards, a connection between herbicide exposure and unfortunate outcomes of pregnancy including congenital anomalies.

This very inclusive approach of Ngo and co-authors gives similar weight to essentially unreviewed abstracts presented years ago as well as to current, and much more detailed, investigations subject to scientific peer review. This review fails to inform the reader as to the social and political aspect of their argument. The possible human health effects in Vietnam of exposure to dioxin are intertwined with concerns about, and revulsion at, 'chemical and ecological warfare'. Accordingly visitors to Vietnam are taken to 'Peace Villages' where they are shown malformed children whose problems are ascribed to herbicide exposure without any sort of scientific proof. At Tu Du Obstetrical hospital in Ho Chi Minh City there is a large collection of preserved 'monsters'; such a collection can commonly be found in similar institutions throughout the world. It is widely believed that these fetal deformities are the result of herbicide exposure but again without any sound scientific evidence. Vietnamese 'Victims of Agent Orange' are currently in court in the US and the herbicide aetiology of their specific injuries is assumed without any good scientific basis. The case was dismissed on legal grounds and is currently on appeal.⁸

We are of the opinion, based on research beginning even before 1970, that there is no doubt as to the toxicity of the dioxin contaminant of Agent Orange.^{5,6,9–11} This dioxin has resulted in serious health effects in humans. We, and many others, have shown elevated levels of TCDD in some Vietnamese, although none of them are now as high as they were in 1970.^{12–18} At some locations in the south of Vietnam small populations are still being poisoned by the continued

consumption of residual dioxin in their diet. There is no doubt that during and after the war, many Vietnamese absorbed this very toxic material. It is our belief from toxicological research and epidemiological studies from many countries that this dioxin probably resulted in significant health effects in Vietnam. However we are not convinced that Vietnamese investigations linking congenital malformations to dioxin are, as yet, more than suggestive. We know of no non-Vietnamese studies linking herbicide or dioxin exposure to congenital malformations other than spina bifida and anencephaly. Earlier Vietnamese studies or case reports suggested a link to liver cancer and to hydatidiform mole and choriocarcinoma, but these did not hold up after more rigorous subsequent research by Vietnamese and Western scientists.^{19,20} This article and its novel approach confirm the need for continued rigorously controlled research to definitively answer the question posed at the opening of this commentary. To date the answer is, at best, scientifically equivocal and, at worst, without valid positive scientific evidence.

References

- 1 Ngo AD, Taylor R, Roberts CL, Nguyen TV. Association between Agent Orange and birth defects: systematic review and meta-analysis. *Int J Epidemiol* 2006;**35**:1220–30.
- 2 Proceedings of the First International Conference on Agent Orange and dioxin. Ho Chi Minh City, Vietnam, 1983.
- 3 Proceedings of the Second International Conference on Agent Orange and dioxin. Hanoi, Vietnam, 1994.
- 4 Institute of Medicine. *Veterans and Agent Orange: Update 2004*. Institute of Medicine of the National Academies Press, 2005.
- 5 Schecter A, Gasiewicz TA (eds). *Dioxins and Health*. 2nd edn. Hoboken, NJ: John Wiley & Sons, 2003.
- 6 US Environmental Protection Agency. Draft Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. 2000. Available at: <http://www.epa.gov/NCEA/pdfs/dioxin/index.htm> (Accessed April 27, 2006).
- 7 Constable JD, Hatch MC. Reproductive effects of herbicide exposure in Vietnam: recent studies by the Vietnamese and others. *Teratog Carcinog Mutagen* 1985;**5**:231–50.
- 8 Agent Orange Product Liability Litigation, 373 F.Supp.2d 7 (E.D.N.Y. 2005); Vietnam Association for Victims of Agent Orange/Dioxin, et al. v. Dow Chemical Co., United States Court of Appeals for the Second Circuit, Docket No. 05-1953-cv.
- 9 Agency for Toxic Substances and Disease Registry. Toxicological profile for chlorinated dibenzo-p-dioxins (update). Atlanta, GA: Agency for Toxic Substances and Disease Registry, 1998.
- 10 National Toxicology Program (NTP). *9th Report on Carcinogens 2000 (Revised January 2001)*. National Toxicology Program, 2001.
- 11 World Health Organization International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 69: Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. Lyon: IARC, 1997.
- 12 Baughman R, Meselson M. An analytical method for detecting TCDD (Dioxin): levels of TCDD in samples from Vietnam. *Environ Health Perspect* 1973;**5**:27–35.
- 13 Dwernychuk LW, Cau HD, Hatfield CT *et al.* Dioxin Reservoirs in Southern Vietnam—a legacy of Agent Orange. *Chemosphere* 2002;**47**:117–37.
- 14 Schecter A, Dai LC, Pöpke O *et al.* Recent dioxin contamination from Agent Orange in residents of a Southern Vietnam City. *J Occup Environ Med* 2001;**43**:435–43.
- 15 Schecter A, Dai LC, Thuy LT *et al.* Agent Orange and the Vietnamese: the persistence of elevated dioxin levels in human tissues. *Am J Public Health* 1995;**85**:516–22.

- ¹⁶ Schecter A, Pavuk M, Constable JD, Dai LC, Pöpke O. A follow-up: high level of dioxin contamination in Vietnamese from Agent Orange, three decades after the end of spraying. *J Occup Environ Med* 2002;**44**:218–20.
- ¹⁷ Schecter A, Quynh HT, Papke O, Tung KC, Constable JD. Agent Orange, Dioxins, and Other Chemicals of Concern in Vietnam: Update 2006. *J Occup Environ Med* 2006;**48**:408–413.
- ¹⁸ Schecter A, Birnbaum L, Ryan JJ, Constable JD. Dioxins: an overview. *Environ Res* 2006; Epub ahead of print.
- ¹⁹ Cordier S, Le TB, Verger P *et al.* Viral infections and chemical exposures as risk factors for hepatocellular carcinoma in Vietnam. *Int J Cancer* 1993;**55**:196–201.
- ²⁰ Ha M-C, Cordier S, Bard D *et al.* Agent Orange and the risk of gestational trophoblastic disease in Vietnam. *Arch Environ Health* 1996;**51**:368–74.