8. Wartenberg D, Simon R. Comment: integrating epidemiologic data into risk assessment. *Am J Public Health.* 1995;85:491–493.
9. Land CE. Estimating cancer risks from low doses of ionizing radiation. *Science.* 1980; 209:1197–1203.
10. Greenland S, Morgenstern H. Ecological bias, confounding, and effect modification. *Int J Epidemiol.* 1989;18:269–274.
11. Stidley CA, Samet J. A review of ecologic studies of lung cancer and indoor radon. *Health Phys.* 1993;65:234–251.
12. Greenberg HL, Ott M, Shore R. Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: a mortality study. *Br J Indust Med.* 1990;47:221–230.
13. Rinsky RA, Melius J, Hornung R, et al. Case-control study of lung cancer in civilian employees at the Portsmouth Naval Shipyard, Kittery, Maine. *Am J Epidemiol.* 1988;127:55–64.
14. Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. *Epidemiology.* 1994;5:189–196.
15. Robins JM, Blevins D, Ritter G, Wulfsohn M. G-estimation of the effect of prophylaxis therapy for pneumocystis carinii pneumonia on the survival of AIDS patients. *Epidemiology.* 1992;3:319–336.
16. Doll R, Peto R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J Epidemiol Community Health.* 1978;32:303–313.
17. Walker AM. Declining relative risks for lung cancer after cessation of asbestos exposure. *J Occup Med.* 1984;26:422–426.
18. National Academy of Sciences/National Research Council. *Health Risks of Radon and Other Internally Deposited Alpha-Emitters (BEIR IV).* Washington, DC: National Academy Press; 1988.
19. Filkelstein MM. Use of "time windows" to investigate lung cancer latency intervals at an Ontario steel plant. *Am J Indust Med.* 1991;19:229–235.
20. Collingwood K, Pasternack B, Shore R. An industry-wide study of respiratory cancer in chemical workers exposed to chloromethyl ethers. *J Natl Cancer Inst.* 1987;78:1127–1136.
21. Shapiro S. Meta-analysis/shmeta-analysis. *Am J Epidemiol.* 1994;140:771–778.
22. Petitti DB. Of babies and bathwater. *Am J Epidemiol.* 1994;140:779–782.
23. Greenland S. Can meta-analysis be salvaged? *Am J Epidemiol.* 1994;140:783–787.
24. Greenland S. Invited commentary: a critical look at some popular meta-analytic methods. *Am J Epidemiol.* 1994;140:290–296.

Editorial: Agent Orange in Vietnam

Few issues manifest the ideological divisions in our society as powerfully as the Vietnam War, and no public health issue is more entangled with our unease about that war than the health effects of dioxin. While the war and the dissension at home were still raging, Bertrand Russell charged that the US military was using carcinogenic herbicides in Vietnam. US newspapers responded with editorials stating that the eminent mathematician may be suffering from senility. Ironically, Admiral Zumwalt (who gave the order to use herbicides for tactical purposes in Vietnam) reportedly has come to believe that his son's early death from lymphoma was due to herbicide exposure in Vietnam. He nevertheless defends his decision as appropriate, given the American lives presumed saved by defoliation.

It may be because enough time has transpired since the war, and because our understanding of the relation between economic activity and environmental protection has sufficiently progressed, that we can approach the issue of the health effects of dioxin with some objectivity—even among the Vietnamese. Fortunately, our efforts in this regard can be informed by a much more substantial body of evidence than earlier efforts. The ideological nature of earlier evaluations was fueled, at least in part, by the scarcity of toxicologic and epidemiologic data directly relevant to the issue.

A report in this issue of the Journal[1] provides some new data in this regard. These data come from a group of scientists who have struggled for many years, usually without adequate funding, to measure dioxin levels in breast milk, adipose tissue, and blood from Vietnamese. Although these data are not from a systematic epidemiologic design—there may be problems with the representativeness of the samples selected, potential problems with the handling of samples, and so on—outright fraud would be necessary to artifactually produce the clear difference reported between persons residing in unsprayed (northern) and sprayed (southern and central) areas of Vietnam. The mean 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) blood level is 6 times greater in the southern/central group than in the northern. This large discrepancy is not found for other specific congeners of the higher chlorinated dioxins or furans, although the other congeners are generally higher in concentration in the sprayed areas. Since TCDD was the major dioxin-like contaminant in Agent Orange (a mixture of 2,4,5-trichlorophenoxyacetic acid [2,4,5-T] and 2,4-dichlorophenoxyacetic acid [2,4-D]), these findings suggest that the TCDD in 2,4,5-T may have found its way into the food chain of some Vietnamese. The elevated levels fron 1984 to 1992 may reflect much higher body burdens in the past and persistence of TCDD in the environment.

Is there a plausible alternative source of elevated TCDD in southern Vietnam? In this regard, it is of interest that the mean TCDD level in adipose tissue of 15 parts per trillion (ppt) in the southern samples is three times greater than the 5 ppt found in an epidemiologic study of samples in the United States.[2] The blood levels also exceed those reported for US samples by a factor of 3 (13 ppt vs 4 ppt).[3] Given the current theory that environmental TCDD results primarily from industrial processes,[4] it is difficult to identify plausible alternative sources of TCDD in the environment of southern Vietnam that would produce levels exceeding those in the US.

If we accept that there is some subpopulation in Vietnam with protracted exposure to TCDD, then the next important question concerns the evidence of adverse health effects of such exposure. More precisely, at what concentration of TCDD in blood or tissue does the risk of adverse effects increase and by how much? There is now a substantial body of animal and epidemiologic data that addresses this question, especially in the case of cancer outcomes.

Treatment with TCDD has been associated with increased neoplasms in every animal bioassay reported in the scientific literature.[5] These carcinogenicity models have included several species and tumors at multiple sites. Furthermore, carcinogenic effects occur at concentrations as low as 1.4 ng/kg per day. The carcinogenicity of TCDD has also been reported for the Syrian Hamster[6]—a finding of particular importance since hamsters, like humans, are relatively resistant to the acute toxic effects of TCDD.

Editor's Note. See related article by Schecter et al. (p 516) in this issue.

Although epidemiologic studies are inherently more subject to confounding and sampling bias than laboratory studies, the two major cohort studies of chemical workers with sufficient measures of TCDD in tissue to verify chronic exposure have yielded results consistent with the animal data. The study in the US by the National Institute for Occupational Safety and Health found a 50% increase in total cancer mortality among more heavily exposed workers with latency of at least 20 years.[13] A study of workers from a plant in Hamburg, Germany, also found an increase in cancer mortality.[7] Ten years of work in the 2,4,5-T production section of the Hamburg plant was associated with a 170% increase in total cancer mortality.[8] The Hamburg study also included sufficient information to relate work history to TCDD levels in blood or tissue.[9] The most heavily exposed decile of men, with estimated tissue TCDD levels averaging 760 ppt during exposure, showed a three to fourfold increase in cancer mortality. Finally, a third study of a group of chemical workers with acute exposure to TCDD (resulting from an accident) found a twofold increase in total cancer mortality after a latency of 20 years.[10]

The significance of these epidemiologic findings is underscored by the fact that, to our knowledge, no other occupational exposure has been shown by the epidemiologic method to elevate significantly both all-cause mortality and total cancer mortality (as found in the Hamburg study). These epidemiologic findings are thus consistent with the animal data indicating that TCDD is a potent carcinogen at multiple sites across mammalian species.

There is also consistency across epidemiologic studies focusing on TCDD and the risk of soft tissue sarcoma. Hardell was the first to report a link between sarcomas and exposure to phenoxy acids and chlorophenols.[11] His studies were severely criticized by chemical industry representatives. In fact, Richard Doll reviewed a report by the Monsanto Corporation and concluded that Hardell's papers should no longer be considered part of the scientific literature.[12] However, subsequent studies have replicated the relation between exposure to TCDD-contaminated substances and soft tissue sarcoma[13–16]; and the confirming studies include an additional one from New Zealand[17,18] if the analyses are restricted to farmers. Professor Doll has resumed citation of Hardell's papers,[19] and Olav Axelson has argued that fraud occurred in two industry reports that misclassified soft tissue sarcoma and malignant lymphoma cases as unexposed to TCDD.[20]

Despite earlier reviews to the contrary, there has been little corroboration of Hardell's hypothesis that the risk of malignant lymphoma is strongly related to TCDD. Thus, although some inconsistencies across epidemiologic studies persist, and although the epidemiologic method itself cannot entirely remove the specter of misleading associations due to confounding, the evidentiary pendulum has swung toward substantiation of the carcinogenicity of TCDD-contaminated compounds in humans. Given that TCDD is a strong tumor promoter at multiple sites, and that different studies may involve different combinations of exposures to other carcinogens, some epidemiologic inconsistencies are likely to remain.

Progress has also been made in unraveling the mechanism of TCDD carcinogenicity in animal models. It appears to be a powerful promoter, but only a weak initiator. For example, tumors were produced in 100% of hairless mice treated with the initiator *N*-methyl-*N*-nitrosoguanadine after a series of 30-ng dosages of TCDD.[21] There is also mounting evidence that the aryl hydrocarbon (Ah) receptor mediates TCDD effects, that it modifies some receptor systems which are involved in cell growth and differentiation, and that hormones, especially estrogens, influence the carcinogenic action[5] of TCDD. More recently, there is some evidence that TCDD increases oxidative stress and lipid peroxidation.[22] Enhanced oxidative stress could play a role in many disease processes, including carcinogenesis and atherogenesis.[23] Recent findings from the Hamburg cohort are consistent with these animal data on oxidative stress. Extended follow-up has revealed not only an increased risk of total and cancer mortality, but a marked elevation in ischemic heart disease mortality among the heavily exposed.[24] Thus, although the epidemiologic data are most compelling for increased cancer risk, there is considerable animal and epidemiologic evidence to indicate that increased cancer morbidity may be only a portion of the adverse health effects of heavy TCDD exposure. Furthermore, these very broad effects across sites and diseases suggest a fundamental pathologic mechanism such as increased oxidative stress and compromise of the immune system.

In the case of epidemiologic findings, it is difficult to limit causal attribution to TCDD itself. For example, phenoxy acids not contaminated with TCDD may be carcinogenic in humans. This is suggested by studies of chemical workers[25] and by the finding in a randomized trial that treatment with clofibrate (a chlorinated phenoxypropionic acid derivative used as a lipid lowering agent) was associated with increased cancer mortality.[26]

2,3,7,8-TCDD is considered to be the most toxic member of a class of compounds made up of polychlorinated dioxins (CDDs), furans (CDFs) and biphenyls (PCBs)—which are a subclass of halogenated aromatic hydrocarbons. Dioxins and furans are made up of two benzene rings connected by a pair of oxygen atoms (dioxins) or a single oxygen atom (furans); PCBs also include two benzene rings that can take on a dioxin-like structure. Each of the hundreds of specific congeners in this class is determined by the number and position of halogen substitutions. Processes that produce dioxin-related compounds usually produce more than one member of this class. And what is known of the toxicology of these compounds suggests that their toxic action may operate via the Ah receptor, with differences between congeners only in the slope of the dose-response relations. However, toxicologic evaluation of only a few congeners is available. Furthermore, TCDD in animal models is a much more potent promoter than initiator. So it is also plausible that the carcinogenic response to TCDD exposure in humans is dependent upon exposure to other initiators. These considerations are of relevance to any plans to conduct epidemiologic studies in Vietnam. The cocktail of cocarcinogens may determine the pattern and extent of TCDD effects on cancer risk.

Given these findings and qualifications, do the levels of TCDD reported in Vietnamese by the current authors suggest a substantial increase in cancer risk? Since the sampling of persons and groups was from pooled specimens and not representative, it is not possible to determine the body burden of any particular population in Vietnam. However, if we use the Hamburg results to extrapolate,[9] then persons with tissue or blood lipid TCDD levels above 500–600 ppt (presumably during actual spraying in the 1960s) are at dramatically increased risk of cancer. Given the TCDD levels of 630–1570 ppt reported in samples of human milk lipid in 1970, it is then plausible that there is a subpopulation in Vietnam at very elevated cancer risk. This increased

risk may apply to a number of other adverse outcomes as well. Pooled blood samples with TCDD levels of 33 ppt in 1992 could, depending upon the distribution of levels in individuals, include a subset of up to 15% with earlier heavy exposures. (Tissue concentrations of TCDD in humans decline by 50% every 6 to 7 years after exposure ceases.) These high level exposures could have resulted from consumption of TCDD-contaminated food for several years during the period of spraying. There may be, however, only a small number of such persons. The number and distribution of exposure using biomarkers remain to be determined by systematic epidemiologic studies.

At this point, it appears that Bertrand Russell's charge that the US military was spraying carcinogenic herbicides in Vietnam was correct. In our view, it is now time to determine systematically the distribution and extent of TCDD exposure in Vietnam and, if substantial, assess health effects and seek preventive interventions. Vietnam may have more pressing public health problems on which to focus, but many in the United States may feel a special responsibility to join the ongoing research efforts by inadequately funded investigators from European and other countries, especially those from France and the World Health Organization's International Agency for Research on Cancer. It is also the case that scientific information about TCDD effects gleaned from studies in Vietnam will help industrialized nations attempting to deal with widespread contamination by dioxin and related compounds in their own environments. Regardless of our intentions, Agent Orange may still be operative in Vietnam. □

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References

1. Schecter A, Dai LC, Thuy LTB, et al. Agent Orange and the Vietnamese: the persistence of elevated dioxin levels in human tissues. *Am J Public Health.* 1995;85: 516–522.
2. *Chlorinated Dioxins and Furans in the General US Population: National Human Adipose Tissue Survey.* Washington, DC: Environmental Protection Agency, 1990.
3. Schecter A, Päpke O, Lis A, Ball M. Chlorinated dioxin and dibenzofuran levels in US human placentas and fetal tissue in comparison with US adult population dioxin levels. In: Fiedler H, Hutzinger O, Birnbaum L, Lambert G, Needham L, Safe S, eds. *Dioxin '94: 14th International Symposium on Chlorinated Dioxins, PCB and Related Compounds.* Kyoto, Japan; 1994:66–66.
4. Smith RM, O'Keefe PW, Aldous KM, Briggs R, Hilker DR, Connor S. Measurement of PCDFs and PCDDs in air samples and lake sediments at several locations in upstate New York. *Chemosphere.* 1992; 25(1–2):95–98.
5. Lucier G, Clark G, Hiremath C, Tritscher A, Sewall C, Huff J. Carcinogenicity of TCDD in animals. *Toxicol Indl Health.* 1993;9:631–668.
6. Rao MS, Subbarao V, Prasad JD, Scarpelli DC. Carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the Syrian golden hamster. *Carcinogenesis.* 1988;9:1677–1679.
7. Manz A, Berger J, Dwyer JH, Flesch-Janys D, Nagel S, Waltsgott H. Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet.* 1991;338:959–964.
8. Dwyer JH, Flesch-Janys D, Berger J, Manz A. Duration of occupational exposure to dioxin contaminated substances and risk of cancer mortality. *Am J Epidemiol.* 1992;136: 1018.
9. Flesch-Janys D, Berger J, Manz A, Nagel S, Waltsgott H. Quantification of exposure to dioxins and furans in a cohort of an herbicide producing plant in Hamburg. *Chemosphere.* 1994;25:1021–1028.
10. Zober A, Messerer P, Huber P. Thirty-four year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. *Int Arch Occup Environ Health.* 1990;62:139–157.
11. Hardell L, Sandström A. Case control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br J Cancer.* 1979;39:711–717.
12. Young AL, Reggiani GM, eds. Agent Orange and Its Associated Dioxin: Assessment of a Controversy. Amsterdam, The Netherlands: Elsevier Science Publishers; 1988.
13. Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA. Cancer mortality in workers exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin. *N Engl J Med.* 1991;324: 212–218.
14. Bertazzi PA, Zocchetti C, Pesatori AC, Guercilena S, Sanarico M, Radice L. Ten-year mortality study of the population involved in the Seveso Incident in 1976. *Am J Epidemiol.* 1989;129:1187–1200.
15. Bertazzi PA, Zocchetti C, Pesatori AC, Guercilena S, Sanarico M, Radice L. Mortality in an area contaminated by TCDD following an industrial incident. *Med Lav.* 1989;80:316–29.
16. Saracci R, Kogevinas M, Bertazzi PA, et al. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet.* 1991;338:1027–1032.
17. Smith AH, Fisher DO, Giles HJ, et al. The New Zealand soft tissue sarcoma case-control study: interview findings concerning phenoxyacetic acid exposure. *Chemosphere.* 1983;12:565–571.
18. Smith AH, Pearce NE, Fisher DO, et al. Soft tissue sarcoma and exposure to phenoxyherbicides and chlorophenols. *JNCI.* 1984;73:1111–1117.
19. Doll R. Are we winning the fight against cancer? An epidemiologic assessment. *Eur J Cancer.* 1990;26:500–505.
20. Axelson O. Exposure to phenoxy herbicides and chlorinated dioxins and cancer risk: an inconsistent pattern of facts and frauds? In: Renzoni A, Mattei N, Lari L, Fossi MC, eds. *Contaminants in the Environment.* Boca Raton, Fla: Lewis Publishers; 1994:213–220.
21. Poland A, Palen D, Glover E. Tumor promotion by TCDD in skin of HRS/J mice. *Nature.* 1982;300:271–273.
22. Alsharif NZ, Hassoun E, Bagchi M, Lawson T, Stohs SJ. The effects of anti-TNF-alpha antibody and dexamethasone on TCDD-induced oxidative stress in mice. *Pharmacology.* 1994;48:127–36.
23. Brewster DW, Bombick DW, Matsumura F. Rabbit serum hypertriglyceridemia after administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). *J Toxicol Environ Health.* 1988;25:495–507.
24. Flesch-Janys D, Berger J, Gurn P, et al. Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from an herbicide plant in Hamburg, Germany. *Am J Epidemiol.* In press.
25. Lynge E. Cancer in phenoxy herbicide manufacturing workers in Denmark, 1947–87—an update. *Cancer Causes Control.* 1993;4:261–72.
26. Committee of Principal Investigators. WHO cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. *Lancet.* 1980;ii:379.