

EXHIBIT 69

Rough First Draft
NHL Proposal for ECPA

In the March 1999 issue of the journal *Cancer*, Hardell and colleagues reported a non-Hodgkin's lymphoma (NHL) case control study that focused on pesticides as potential etiologic factors.¹ The study included 404 NHL cases, diagnosed during the period 1987-1990, from the four most northern counties of Sweden. These cases and 741 controls were mailed an 18 page questionnaire that requested information about a variety of factors including pesticide use. There was no pesticide exposure assessment, per se, in this study. Exposure was presumed based on reported use of specific pesticides.

The authors found statistically significant associations between NHL and reported use of any herbicide, reported use of any fungicide, and reported use of the herbicide MCPA. Non significant associations were reported for other herbicides, including glyphosate. The authors interpreted their results as supportive of a role for chemical pesticides as causes of NHL. They speculated, since NHL is known to be elevated among transplant patients², that phenoxyacetic acids might suppress immunity leading to increased risk of NHL. In fact, they interpreted selected papers from the literature as supportive of an immunotoxic effect for phenoxyacetic acids and chlorophenols.^{3,4,5}

There are obvious scientific limitations to this work, some of which have been pointed out elsewhere.^{6,7,8} Nonetheless, this study garnered media attention worldwide. It is probably not important in and of itself, but rather assumes importance to industry as a sentinel of other, similar studies soon to come. In some ways the study is a throwback to similar studies by Hardell^{9,10} in 1979 and 1981 that led to a series of studies by the U.S. National Cancer Institute focused on phenoxy herbicides and NHL.^{11,12} These studies all found questionable associations between phenoxy herbicide exposure and NHL. As a result, the largest U.S. lawn treatment company stopped using 2,4-D, though a scientific advisory body convened by the U.S. Environmental Protection Agency did not consider the available studies as good evidence for a causal relationship between phenoxy herbicides and NHL.¹³

Hardell's most recent study¹ comes at a time when the U.S. National Cancer Institute is getting ready to begin publishing papers from their prospective Agricultural Health Study of 60,000 farmers and their families. Thus, the stage is set for another round of epidemiologic studies to cause significant concern for industry.

One of the common denominators of epidemiologic research in the pesticide/NHL area is that the investigators' publication records - both their original studies and their review articles - indicate a conviction that pesticides cause NHL (and other human cancers). Thus, the field is unbalanced in terms of the a priori beliefs of researchers - an important factor in how subsequent data will be interpreted. Industry, in the past, has declined to support agricultural epidemiologic research - though there is an ongoing U.S. industry effort, through the American Crop Protection Association, to assess exposures, through urinary biomonitoring, for farmers and their families.

Monsanto scientists, during discussions with academic experts about Hardell's most recent study, were asked whether industry would consider supplying supplemental funding to support an agricultural chemical exposure assessment as part of an ongoing nationwide NHL study in Sweden and Denmark. The study is being conducted by Dr. Hans-Olov Adami (from the Karolinska Institute and the Harvard School of Public Health) and colleagues. Dr. Adami is neutral on the issue of agricultural chemicals and NHL and, in the past, he did a valuable published literature review for industry that cast doubt on the chlorinated compounds/cancer hypothesis. He is very interested in delving into the reasons (e.g. bias, confounding factors) why epidemiologic studies tend to associate pesticides and NHL.

There are a number of reasons why industry should consider this proposal seriously. First, allegations that pesticides cause cancer are important to the business and regulatory climate for pesticide manufacturers and, indeed, companies have a product stewardship obligation to ensure that their products can be used safely. Second, NHL is the cancer that has been most often "linked" to pesticides. Third, neutral researchers will be a scarce commodity without industry support for agricultural epidemiologic research - especially researchers of the stature of Dr. Adami. Lastly, the pressure from epidemiologic findings is sure to escalate over the next few years as papers start to be published from the National Cancer Institute's Agricultural Health Study. Given the long lead time required to conduct epidemiologic research, industry must be proactive in order to be influential in this area.

Supporting this proposal will require a substantial financial commitment, perhaps more than \$1M. However, the economic consequences of adverse, unopposed epidemiologic findings can dwarf the funding needed for this project.

It can be arranged to have Dr. Adami circulate a formal proposal and meet with industry scientists if there is interest in evaluating this proposal more specifically.

Respectively submitted,

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References

1. Hardell L, Eriksson M. A Case-control Study of non-Hodgkin Lymphoma and Exposure to Pesticides. *Cancer* 1999;85:1353-1360.
2. Newstead CG. Assessment of risk of cancer after renal transplants. *Lancet* 1998;351:610-611.
3. Faustini A, Settini L, Pacifici R, Fano V, Zuccaro P, Forastiere F. Immunological changes among farmers exposed to phenoxy herbicides: preliminary observations. *Occup Environ Med* 1996;53:583-585.
4. Exon JH, Koller LD. Effects of chlorinated phenols on immunity in rats. *Int J Immunopharmacol* 1985;7:239-247.
5. Daniel V, Huber W, Bauer K, Opelz G. Impaired in-vitro lymphocytes responses in patients with elevated pentachlorophenol (PCP) blood levels. *Arch Environ Health* 1995;50:287-292.
6. Acquavella JF, Cullen MR, Farmer D. re: re: A Case-control Study of non-Hodgkin Lymphoma and Exposure to Pesticides. (letter to the editor) *Cancer* 1999;86:729-730.
7. Cullen MR. Review of the Hardell Study for Monsanto Company, 1999.
8. Adami HO, Trichopoulos D. Review of the Hardell Study for Monsanto Company, 1999.
9. Hardell L, Malignant lymphomas of the histiocytic type and exposure to phenoxyacetic acids or chlorophenols. *Lancet* 1979;I:55-56.
10. Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols, and phenoxy acids: a case control study. *Brit J. Cancer* 1981;43:169-176.
11. Hoar SK, Blair A, Holmes FF, et al. Agricultural herbicide use and risk of lymphoma and soft tissue sarcoma. *JAMA* 1986;256:1141-1147.
12. Hoar Zahm S, Weisenburger DD, Babbit PA, et al. A case control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* 1990;1:349-356.
13. Environmental Protection Agency, An SAB Report: Assessment of potential 2,4-D carcinogenicity. Review of the

epidemiological and other data on potential carcinogenicity of 2,4-D by the SAB/SAP joint committee. EPA-SAB-EHC-94-005, Washington, DC: US EPA; 1994.