

**From:** ACQUAVELLA, JOHN F [AG/1000]

**Sent:** 02 September 2003 21:29

**To:** CARR, KATHERINE H [AG/1000]; GOLDSTEIN, DANIEL A [AG/1000]; FARMER, DONNA R [AG/1000]; GARNETT, RICHARD P [AG/5040]; KRONENBERG, JOEL M [AG/1000]

**Cc:** WRATTEN, STEPHEN J [AG/1000]; MARTENS, MARK A [AG/5040]; BROECKAERT, FABRICE [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; DANHAUS, ROY G [AG/1000]

**Subject:** RE: Article re: NHL and glyphosate, alachlor

Thanks to Kathy for bringing the De Roos et al. paper to our attention (see below). I have a few quick thoughts about it. More information will follow.

This is a paper from investigators at the National Cancer Institute (NCI). For those of you who don't know the history of the NCI's agricultural epidemiology research, the present paper is a reanalysis of data from the Kansas, Nebraska, and Minnesota/Iowa studies from the mid-1980s. It surprises me greatly that they would spend such effort on this old and limited dataset, when they are collecting and analyzing data from the Agricultural Health Study. A fair amount of the data in these old studies came from next-of-kin respondents and is of questionable accuracy. Others have shown that next-of-kin of cancer cases tend to over-report pesticide use. Accordingly, they should have done some analyses segregating out the next-of-kin information, but they didn't.

What's new in this paper is that the investigators use a form of regression analysis that weights prior information (like in a Bayesian analysis) to influence measures of association. The lead author specialized in this type of analysis for her PhD dissertation and she did a postdoc at NCI. Relatively few people have much experience with this analysis, but it is said to be more conservative when doing multiple comparisons (viz. yields fewer false positives).

It is interesting that this analysis did not find an association between NHL and 2,4-D. The Kansas and Nebraska studies are always cited as evidence that 2,4-D does cause NHL. Unfortunately, the authors get into a bit of a convoluted argument in order to avoid saying that their most recent analyses seems to refute much of what they have said previously about 2,4-D.

It is clear that alachlor is near the top of the investigator's list of pesticides that might cause NHL, even though alachlor seemed not to be related to NHL in this analysis (see Table 3). As you know, the NCI Ag Health Study team has a soon to be published paper that shows a weak relationship between reported use of alachlor and lymphopoietic cancers.

Strangely, glyphosate looks to be one of the pesticides most associated with NHL in this analysis (see Table 3). At the time these NHL cases were diagnosed (1979-83), glyphosate was very early in its commercial history. Not only doesn't the association between glyphosate and NHL make sense given glyphosate's toxicology profile, but it doesn't make sense on a timing of exposure basis - one expects a fairly long period between exposure and related cancers for other than extremely potent carcinogens. I did note that De Roos et al. misclassified glyphosate in Table 1 as to its carcinogenic probability (they had it as 0.3, same as alachlor, when it should have been 0.1). Had it been classified correctly, the odds ratio in the last column of Table 3 would have been lower (perhaps much lower).

The authors spent an entire paragraph in the discussion on glyphosate, specifically mentioning the Hardell and McDuffie studies:

Glyphosate, commercially sold as Roundup, is a commonly used herbicide in the United States, both on crops and non-cropland areas.<sup>50</sup> An association of glyphosate with NHL was observed in another case-control study, but the estimate was based on only four exposed cases.<sup>51</sup> A recent study across large region of Canada found an increased risk of NHL associated with glyphosate use that increased by the number days used per year.<sup>52</sup> These few suggestive findings provide some impetus for further investigation into the potential health effects of glyphosate, even though one review concluded that the active ingredient is non-carcinogenic and non-genotoxic.<sup>53</sup>

I'm afraid this could add more fuel to the fire for Hardell et al.

I'm going to see one of the authors of this paper this weekend at the American College of Epidemiology meeting. I'll ask him about some of these issues.

It looks like NHL and other lymphopoietic cancers continue to be the main cancer epidemiology issues both for glyphosate and alachlor. We're assembling a panel of experts to work on this.

Regards,

John

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-----Original Message-----

**From:** CARR, KATHERINE H [AG/1000]

**Sent:** Tuesday, September 02, 2003 12:39 PM

**To:** ACQUAVELLA, JOHN F [AG/1000]; GOLDSTEIN, DANIEL A [AG/1000]; FARMER, DONNA R [AG/1000]; GARNETT, RICHARD P [AG/5040]; KRONENBERG, JOEL M [AG/1000]

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**Subject:** Article re: NHL and glyphosate, alachlor

See the following recent article, in which glyphosate and alachlor are included:

AJ De Roos, SH Zahm, KP Cantor, DD Weisenburger, FF Holmes, LF Burmeister, and A Blair

**Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men.**

Occup Environ Med 1 Sep 2003 60(9): p. E11.

Link to abstract: [MEDLINE Citation](#)

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