"Birth Malformations and Other Adverse Perinatal Outcomes": Available Data Sources Pose a Dilemma

A recent paper (Schreinemachers 2003) highlights both the opportunities and pitfalls implicit in the use of national public use datasets. Schreinemachers (2003) used the national linked birth and infant death certificate files for calendar years 1995–1997 to study the prevalence and risk factors for adverse perinatal outcomes in high and low wheat-producing counties of four northern Great Plains states. Although Schreinemachers did not clearly state the null hypothesis, she attempted to test the assertion that *in utero* exposure to agricultural herbicides is associated with birth defects, preterm delivery, and small-for-gestational age (SGA) infants. Vital records for residents of 147 rural, agricultural counties were classified into low-wheat and high-wheat areas based on agricultural production statistics, using the median split method. What Schreinemachers (2003) described as an ecologic analysis is perhaps better categorized as a cross-sectional study with a dichotomous exposure variable classified by study-subject residence in a high or low wheat-producing county. This means that neither the exposure (agricultural herbicides) nor the outcome (birth defects) was adequately measured. The study results and discussion emphasized the statistical analyses of associations with congenital anomalies. Schreinemachers' (2003) Table 3 shows no effect of residence in a high-wheat county on preterm or SGA birth, and a modest increase in male infant mortality due to congenital anomalies. Results comparing low or very low birth weight, or overall fetal or infant mortality outcomes between the two groups of counties were not provided. Most of the results focused on overall and subcategories of birth defects (termed "developmental outcomes" in the title of Table 3); although some of the odds ratios are statistically significant, the author made no adjustment for multiple comparisons. Epidemiologists studying birth defects typically avoid analyses in which "births with any anomaly" is the dependent variable (p. 1262) because of the heterogeneity of the conditions thereby grouped together. Schreinemachers (2003) also neglected to include a map of the study counties, leaving the reader to wonder whether other physiographic, demographic, or economic factors might also influence the study findings.

If the primary study hypothesis is that preconceptional or antenatal exposure to agricultural herbicides increases the risk for birth defects across large geographic areas, it should be noted that this study used, at best, proxy measures for both dependent and independent variables. Because Schreinemachers (2003) provided no direct measures of exposure to herbicides, the reader must presume that differences in agricultural activity across counties correlated directly to individual exposures. Schreinemachers (2003) could have provided a reference to a study demonstrating that all residents of agricultural areas have similar levels of biomarkers of exposure to herbicides.

The most troubling aspect of this paper (Schreinemachers 2003) is its reliance on vital statistics for data on the occurrence of congenital anomalies among the birth events analyzed. Although numerous state programs have been developed in the past 15 years, Schreinemachers selected a study area for which statewide, population-based birth defects surveillance programs did not exist in any of the four states during the study period (National Birth Defects Prevention Network 2002). Her arguments concerning data quality are unconvincing and ultimately raise concerns that the study findings will be misinterpreted and misconstrued, and also will lead to similar analyses with methodologic flaws based on assumptions about the completeness, accuracy, reliability, and validity of vital statistics reporting of birth defects. It is not surprising that results in this study mirror that of Garry et al. (1996), given the use of birth certificate reporting of congenital anomalies to measure the outcome variable in both studies.

Regarding data quality, Schreinemachers (2003) cited Watkins et al. (1996), who examined the sensitivity and positive predictive value of birth defects reported on birth certificates in the metropolitan Atlanta, Georgia, area. They found that only 14% of all cases in the comprehensive multisource registry were reported on birth certificates, and that the overall sensitivity (proportion of all birth defects that were identified on birth certificates) was 28%, but ranged from 10% for rectal atresia/stenosis and 19% for Down syndrome to 40% for spina bifida, 47% for omphalocele/gastroschisis, and 86% for anencephaly. Rather than commenting directly on the implications of these results for the present analysis, Schreinemachers (2003) instead discussed the small proportion of birth certificates in the study sample that were unmarked for presence or absence of birth defects, a statistic that has no bearing on the issues of reliability and validity of the key outcome measures. In a study of completeness of ascertainment in the New York Congenital Malformations Registry, Olsen et al. (1996) concluded that the yield from reabstraction of potential cases reported only on birth certificates was not sufficient compared to the time and expense involved. Many other studies have shown how poor vital statistics data are for identifying babies with birth defects, both in missed cases and in misdiagnosed and misclassified cases (e.g., Hexter et al. 1990; Hudome et al. 1994; Piper et al. 1993). For this reason, most birth defects epidemiologists exclude birth certificate-based cases from their analyses, and the National Birth Defects Prevention Network does not regard state databases based solely on vital statistics records as birth defects surveillance programs. Clinical data in vital statistics databases should not be used for multivariate epidemiologic analyses without independent assessment of its reliability and validity, lest scientifically erroneous conclusions be reached (Kirby 1997, 2001).

Schreinemachers' hypothesis (2003) is worthy of operationalization in a more sophisticated, albeit more expensive, study design. The study should be carried out in a region with comprehensive, multisource birth defects and disabilities surveillance records linked to vital records, with agricultural chemical applications cataloged and mapped through the use of a geographic information system. This may necessitate a large prospective study with a longitudinal component or the creation of the disease surveillance and environmental monitoring databases to support a retrospective study. In the meantime, researchers and clinicians should be wary of generalizing from the results of epidemiologic analyses based on birth defects reports obtained solely from vital statistics sources.

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Re: "Birth Malformations and Other Adverse Perinatal Outcomes in Four U.S. Wheat-Producing States"

In a recent paper on birth malformations, Schreinemachers (2003) uses wheat acreage per county as a surrogate for chlorophenoxy herbicide exposure. Previously, increasing cancer mortality rates were observed with increasing wheat acreage in these counties. (Schreinemachers 2000). The difference for both birth defects and cancer in these regions is interesting, but the underlying causes cannot be identified by ecologic studies. We commend the author for acknowledging the limitations of the study design used. However, she did not demonstrate that the subjects in areas of high-wheat and low-wheat production are sufficiently heterogeneous with respect to chlorophenoxy herbicide exposure to explain the differences in observed health end points.

Schreinemachers (2003) cited several studies that demonstrate measurable 2,4-dichlorophenoxyacetic acid (2,4-D) in children and adults related to turf (i.e., lawn) applications and other home exposure routes (Harris and Solomon 1992; Hill et al. 1989; Nishioka et al. 1996, 2001).

We accept that women and their partners in both the high- and low-wheat producing counties have potential for exposure to herbicides. In the current study, Schreinemachers (2003) used production volume of a single crop to assert that the women and partners living in the high-wheat–producing counties have higher chlorophenoxy exposure, but no data were presented that validate this assumption. A Canadian exposure study (Arbuckle et al. 1999) did identify 2,4-D in the semen of farmers who recently applied 2,4-D, but only among half the applicators. Indeed, results of this exposure study confirmed that applicators are not uniformly exposed and spouses have little or no exposure (Arbuckle et al. 2002, Ritter et al. 1998) Similarly, Curl et al. (2002) concluded that the dust samples of dialkylphosphate, an insecticide metabolite, explained only about 15% of the variability in the children's urine levels. Additional exposure studies, including one by the U.S. Environmental Protection Agency, have similarly concluded that most women and children living on farms have exposure levels consistent with the general, nonfarming populations (Acquavella et al. 2003; Thomas et al. 2002). This suggests a misclassification bias of 50% at least—enough to render the current findings virtually uninterpretable.

How then do we evaluate if the "chemicalization" of our environment poses a risk? Appropriately, Kogevinas and Sala (1998) advocated developing testable hypotheses to evaluate the etiology of birth defects. In contrast, their recommendation of using an ecologic approach still requires that the two groups under study be different with respect to exposure. Risk assessments based on the demonstrated dose–response effects from animal studies predict that widespread low-level exposures should not be associated with an excess risk.

We agree that reducing the incidence of congenital malformations is an important public health challenge. In a recent study designed to determine the reasons for the variability of the reported incidence of congenital heart disease, Hoffman and Kaplan (2002) demonstrated that these variations are primarily caused by differences in detection of minor lesions and by different methods of ascertainment through a variety of diagnostic criteria. Hoffman and Kaplan (2002) concluded that

> given the uncertainties of estimating incidence, there is no evidence that the true incidence of congenital heart disease has changed over the past 50 years, or that it varies in different countries.

The etiologies of birth defects are many and complex, and there is evidence that diagnosis and reporting can vary across regions.

Schreinemachers (2003) offered no data to support that the potential exposure to chlorophenoxy herbicides, much less any actual exposure, is different between the two regions examined. We wonder what other factors that were not studied could contribute to the observed differences in the low-wheat and high-wheat regions.

The authors declare a competing financial interest because they are employed by pesticide-manufacturing companies.

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"Birth Malformations and Other Adverse Perinatal Outcomes": Schreinemachers' Response

The major comments with regard to my paper (Schreinemachers 2003) by Kirby and Salihu and Burns and Leonard refer to the use of ecologic studies to establish causality, use of a surrogate measure of exposure, presence of potential confounders, use of vital statistics as a source of birth malformations, and grouping of malformations based on organ system classifications.

Ecologic studies cannot determine underlying causes of disease, but they can be used to identify potential public health hazards. By using a proxy for chlorophenoxy herbicides, I did offer data to support that potential exposures to chlorophenoxy herbicides and/or contaminants in the two

regions are different, as measured by wheat acreage. If using a proxy measure of exposure was a bad choice, it should have been very difficult to demonstrate effects between low- and high-wheat counties, providing that these effects existed in the first place. Showing that all residents of agricultural areas have similar levels of biomarkers for exposure to herbicides, as Kirby and Salihu would like to see, may be difficult. We may be able to observe effects of exposure only in the most heavily exposed people, as indicated by the presence of 2,4-dichlorophenoxyacetic acid (2,4-D) in semen and blood among a fraction of exposed subjects (Arbuckle et al. 1999; Semchuk et al. 2003).

Both Kirby and Salihu and Burns and Leonard wonder if other factors could have contributed to the observed effects. These confounders would have to be able to cause birth malformations and would also have to be strongly associated with wheat farming. Chlorophenoxy herbicides and/or contaminants are one possible explanation.

I discussed the limitations of using vital statistics as a data source for birth malformations in my paper (Schreinemachers 2003). Grouping of birth malformations with different etiologies would more likely dilute than create existing effects. Although vital statistics are known to be an incomplete source of birth malformations, there is no reason to suspect that this underreporting is associated with wheat farming.

Kirby and Salihu comment on the terminology "ecologic analysis." This is based on the fact that the unit of exposure pertains to geographical areas rather than to individuals (Checkoway et al. 1989). I did not adjust for multiple comparisons, and some of the effects may have been due to chance. However, when effects are observed within a study in different groups of subjects (e.g., boys and girls), or in two independent studies, chance may less likely play a role.

Burns and Leonard state that women and children living on a farm have exposure levels consistent with the general nonfarming population. In my study I compared rural populations in low-wheat regions (including farming and nonfarming families) to those in high-wheat regions. I did not compare families living on farms with families not living on farms; therefore, I do not believe that the argument about 50% misclassification (which likely would have deleted or diluted any effects) applies here. Widespread low-level exposures have not been associated with excess risk, as shown by previous dose–response effects from animal studies. However, we should keep in mind that recent studies indicate that many chemicals have effects at very low levels based on a U-shaped dose–response curve (Welshons et al. 2003). I agree with Burns and Leonard's statement that diagnoses of birth defects can vary across regions, but there is no reason to suspect that wheat farming plays a role.

Kirby and Salihu state that my hypothesis is "worthy of operationalization in a more sophisticated, albeit more expensive, study design." Without my low-resource–intensive, hazard-identifying, hypothesis-generating study, involving a surrogate measure of exposure and utilizing incomplete birth malformation data, we might have never suspected the existence of this potential health problem, and therefore would have no basis to undertake a more labor-intensive and expensive study.

The author declares she has no competing financial interests.

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He Who Pays the Piper Calls the Tune

We live in a bizarre world of previously only imagined "Newspeak" (Orwell 1949) in which the meaning of concepts can be redefined into their antonyms under the eyes of an editor—when a scientist who is employed by a large multinational nuclear technology corporation (BNFL) claims in all seriousness to have no conflict of interest when expressing his opinion in an exchange of letters (Wakeford 2003). The contested issue is what constitutes a valid scientific basis for estimates of radiation risk, which establishes legal rights to compensation for possibly radiation-related detriment among nuclear workers. If the nuclear workers are BNFL (British Nuclear Fuels, Ltd.) employees, the decision whether or not such compensation should be paid by the company would likely be based on scientific advice from the in-house expert, Richard Wakeford.

In a creative twist of logic, this clear conflict of interest is purportedly erased by the fact that the author published a paper in which he "argues for a non-zero risk of cancer at low doses of radiation."

Who pays whom to avoid paying whom?

The author declares he has no competing financial interests.

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Does "He Who Pays the Piper" Really Call the Tune: Wakeford's Response

I respect Nussbaum's right to an opinion, but his letter is misleading. First, I clearly used the address of my employer in my letter and provided a statement addressing what might be considered a conflict of interest. Second, my letter (Wakeford 2003) was in response to one by Wing and Richardson (2002) that incorrectly claimed that an excess risk of childhood cancer was not experienced by the Japanese atomic bomb survivors who were irradiated *in utero*, citing in support a paper that I coauthored (Doll and Wakeford 1997). Third, if Nussbaum contests the conclusions my academic coauthors and I have published in the scientific literature (Doll and Wakeford 1997; Wakeford and Little 2003), he should explain why. Fourth, BNFL (British Nuclear Fuels) and almost all of the other major employers in the U.K. nuclear industry operate a voluntary compensation program jointly with the relevant labor unions (Wakeford et al. 1998). The technical basis of this program is agreed upon between the employer and employee representatives, both advised by their respective experts. If Nussbaum's views were accepted by the scientific community, undoubtedly, they would be seriously considered by these experts.

Nussbaum would better serve science by engaging the issues addressed in my papers.

The author declares a competing financial interest because he is an employee of BNFL, but

the views he expresses here are not necessarily those of his employer.

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Asthma and Air Toxics: Another Potential Source of Positive Bias

In Ralph Delfino's (2002) excellent review article on asthma and air toxics, he stated that positive bias in traffic studies could have resulted from failure to control for socioeconomic status (SES). We would like to point out an additional potential source of positive bias arising from housing characteristics. In our unpublished analysis of 350,000 housing units in Niagara and Erie Counties, New York, using real property data and traffic counts provided by the Greater Buffalo-Niagara Regional Transportation Council, we found that multifamily residences were 1.7 times more likely than single family residences to be within 100 m of a busy road (> 6,000 vehicles/day), residential apartment buildings were 2.0 times more likely, and apartment units above commercial storefronts 3.7 times more likely. Living in apartments is associated with increased exposure to allergens from cockroaches, rodents, and mold, all of which are considered risk factors for asthma (Brugge et al. 2003; Chew et al. 1999).

In our analysis, we found that if hypothetical odds ratios of 1.5 and 1.25 are assumed for apartments and multiple-family residences respectively, a reported odds ratio of 1.5 due to traffic would be adjusted to 1.38. This is a modest effect, but enough to impact studies with borderline significant findings. Of course, this finding applies only to our specific study area and would vary for other study areas. The issue appears most pronounced in urban and suburban neighborhoods developed in the early 1900s, when the construction of streetcar systems and later zoning ordinances served to concentrate apartment buildings along major roads.

Real property data, which has always been in the public domain, is increasingly becoming available electronically, making it convenient to attribute information such as housing type, age, value, and condition to individuals without needing to contact them directly.

In accordance with EHP *policy, Delfino was asked whether he wanted to respond to this letter, but he chose not to do so.*

The authors declare they have no competing financial interests.

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