

## Association between Air Pollution and Adverse Pregnancy Outcomes in Vancouver

In the November 2003 issue of *EHP*, Liu et al. (2003) concluded that "relatively low concentrations of gaseous air pollutants are associated with adverse effects on birth outcomes." Although this may be true from a purely statistical sense, there appear to be limitations of this research that suggest cautious interpretation of the findings.

Liu et al. (2003) evaluated individual-level birth certificate data, which is an improvement over the ecologic designs of past time-series studies on pollution. However, birth records do not contain most of the variables that are important predictors of low weight and preterm births. These include smoking, alcohol and/or drug abuse, low socioeconomic status (SES), small maternal weight or height, complications of the current or previous pregnancy [e.g., pregnancy-induced hypertension, previous low birth weight (LBW), spontaneous abortion], insufficient weight gain during pregnancy, maternal illness (e.g., fever), and job-related exertion (Berkowitz and Papiernik 1993; Holmes and Soothill 1996; Kramer 1987, 2003; Lang et al. 1996; Moore 2003). Many of these are major factors that substantially affect risk. For example, maternal smoking during pregnancy, which has a prevalence of 10–20% in the United States (Ebrahim et al. 2000; O'Campo et al. 1995), is associated with a 2- to 4-fold increase in risk of LBW or growth restriction (Kramer 1987; Lang et al. 1996; Nordentoft et al. 1996). Therefore, there is considerable room for uncontrolled confounding that might account for the small odds ratio of 1.05–1.10 observed by Liu et al. (2003).

Liu et al. (2003) argued that uncontrolled or residual confounding is an unlikely explanation for their results because *a*) there is no evidence that these factors are associated with air pollution; *b*) ecologic measures of SES did not modify the associations; and *c*) "there were only slight differences between crude and adjusted estimates," and "individual characteristics ... did not attenuate the risk estimates." However, these arguments have limitations.

First, there may not be evidence that important risk factors co-vary with pollution, but it seems reasonable that many might correlate with residential location. Liu et al. (2003) linked pollution measurements in 13 census subdivisions to births within those subdivisions. If gaseous pollutant measurements and other factors (e.g., SES, smoking prevalence) co-vary by census

subdivision, then confounding could occur. Second, ecologic measures are poor surrogates for individual-level ones, which can result in confounder misspecification and residual confounding (Greenland 1980; Liu 1988; Marshall and Hastrup 1996; Morgenstern 1998). Third, the individual-level covariates included in some of the models did appear to have substantive impacts. For example, the odds ratio for the association between LBW and first-month sulfur dioxide exposure changed from a crude value of 0.95 to a significant 1.11 after adjustment for confounding. This is a 17% absolute increase in risk and a change in coefficient from  $-0.05$  to  $+0.10$  per 5 ppb. In other instances the adjustment caused a significant elevation to become a deficit (e.g., association between preterm birth and first-month exposure to ozone) or a null value to become a significant protective effect (preterm birth and last-month ozone exposure). This apparent impact of confounding was caused by variables (e.g., maternal age and season of birth) that are weaker risk factors than many missing variables, such as smoking, SES, and weight gain (Berkowitz and Papiernik 1993; Kramer 1987; Lang et al. 1996). This suggests considerable potential for residual confounding.

The findings of Liu et al. (2003) also lack biological coherence with the literature. The authors invoked a biological mechanism for air pollution similar to cigarette smoking. For smoking, the risk is predominantly during the third trimester, primarily from decreased fetal growth, which has been attributed to decreased maternal and fetal nutrition among smokers and hypoxia from inhaled carbon monoxide (Holmes and Soothill 1996; Kramer 1987; Petridou et al. 1990). However, most of the significant increases reported by Liu et al. (2003) were associated with exposures during the first month or trimester, with no effects seen during the third trimester. It is unclear how these early, low-level pollution exposures, which lack the substantive impact of smoking, would alter fetal growth.

Liu et al. (2003) also do not discuss the potential for spurious results due to multiple comparisons. The authors reported 36 associations within the tables, and many more were likely performed, including multipollutant models. Therefore, at least some of the significant results may be due to chance.

In conclusion, the above limitations could easily account for the findings reported by Liu et al. (2003), without invoking novel effects from air pollution.

*The author is employed by ExxonMobil Biomedical Sciences, Inc.*

**John A. Bukowski**  
ExxonMobil Biomedical Sciences, Inc.  
Annandale, New Jersey  
E-mail: john.a.bukowski@exxonmobil.com

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## Air Pollution and Adverse Pregnancy Outcomes: Response

We thank Bukowski for his critical comments on our article (Liu et al. 2003), in which we reported associations between ambient air pollution and adverse pregnancy outcomes in Vancouver, Canada. In recent years, air pollution has come to be recognized as an important risk factor for a number of adverse health outcomes, particularly cardiorespiratory morbidity (Burnett et al. 1997, 2001; Lin et al. 2002, 2003; Yang et al. 2003) and mortality (Burnett et al. 1997; Dockery et al. 1993; Pope et al. 1995; Villeneuve et al. 2003).

The adverse effects of air pollution on pregnancy outcomes, such as low birth weight (LBW), preterm birth, intrauterine growth retardation (IUGR), and developmental anomalies are of increasing concern. Before our study, there were reports of associations between particulate (total suspended particulate) and gaseous (carbon monoxide,

sulfur dioxide, and nitrogen dioxide) air pollutants and adverse pregnancy outcomes from southern California (Ritz et al. 2000, 2002), China (Wang et al. 1997; Xu et al. 1995), and the Czech Republic (Bobak 2000; Dejmek et al. 1999). Replication of these findings in different populations under different conditions of exposure is an important aspect of epidemiologic research, with consistency of results strengthening the weight of evidence for a true association between exposure and outcome.

Data on important predictors of adverse pregnancy outcomes were not available to us for use in our study (Liu et al. 2003). Although numerous risk factors have been identified (including maternal age, parity, infant sex, and season of birth, as well as gestational age and birth weight, in the case of LBW and preterm birth, respectively, which we were able to take into account), our understanding of the etiology of adverse pregnancy outcomes remains far from sufficient (Kramer 2003). The omission of known or unknown risk factors for birth anomalies may lead to uncontrolled or residual confounding of the association between air pollution and adverse pregnancy outcomes, as Bukowski suggests. However, the extent to which residual confounding might occur in our data is unclear. Schwartz and Morris (1995) have argued that the estimated effects of air pollution are unlikely to be confounded by these factors because they are unlikely to be correlated with daily air pollution levels.

Exposure assessment is always a critical factor in environmental epidemiology (Rothman 1993). Like most other studies of air pollution and population health, our study (Liu et al. 2003) relied on ecologic rather than personal indicators of exposure, with average ambient air pollution concentrations determined using one or more fixed site monitors within census areas in Vancouver. Janssen et al. (1998, 1999) have suggested that air pollution levels from outdoor monitoring stations can provide useful surrogates for personal exposure. Exposure misclassification due to the use of fixed site ambient monitors rather than personal dosimeters is likely to underestimate rather than overestimate the effect of air pollution on birth outcomes (Mallick et al. 2002; Zeger et al. 2000).

The weight of evidence that air pollution is causally related to adverse pregnancy outcomes would be considerably increased through understanding of biological mechanisms by which such effects could occur.

Burkowski notes that we (Liu et al. 2003) included a number of statistical tests of the strength of association between air pollution and adverse pregnancy outcomes, and observes that multiple testing raises the

risk of false positives. Our *a priori* strategy for hypothesis testing focused on predetermined stages of pregnancy (month or trimester), which are thought to represent periods of differential susceptibility to exogenous exposures. Findings from both epidemiologic and toxicologic studies suggest that the fetus is most susceptible to the effects of air pollution during the first trimester (Generoso et al. 1987; Rutledge 2000). Human studies also have suggested that initial changes leading to IUGR might be triggered in early pregnancy, around the time of implantation (Duvekot et al. 1995; Khong et al. 1986). Air pollutants may be absorbed into the maternal bloodstream, cross the placental barrier, and have direct toxic effects on the fetus.

Our *a priori* strategy for the development of appropriate risk models focused on single-pollutant models, with adjustment for relevant covariates available to us, as we reported in Tables 4–7 (Liu et al. 2003). Our strategy also called for an assessment of the robustness of the associations between pregnancy outcomes and specific pollutants against adjustment for copollutants. Although this strategy does involve a moderately large number of statistical tests of the significance of logistic regression coefficients associated with specific pollutants, our evaluation of the data is based more on the evidence provided by this set of hypothesis tests as a whole, rather than on the results of individual tests alone.

Overall, our data suggest that adverse pregnancy outcomes are associated with exposures to air pollutants during pregnancy, particularly in early gestation. Because of limitations of our study, we (Liu et al. 2003) concluded that

“these effects require further examination in other populations, and further research also needs to be conducted with more detailed information on personal exposures, effect modifiers, and other adverse pregnancy outcomes such as birth defects and spontaneous abortion.”

Our data need to be interpreted in the context of the emerging body of scientific evidence on air pollution and adverse pregnancy outcomes, to which we have made a contribution.

*The authors declare they have no competing financial interests.*

**Shiliang Liu  
Daniel Krewski  
Yuanli Shi  
Yue Chen**

Faculty of Medicine  
University of Ottawa  
Ottawa, Ontario, Canada  
E-mail: sliu@uottawa.ca

**Richard T. Burnett**  
Healthy Environments and Consumer  
Safety Branch  
Health Canada  
Ottawa, Ontario, Canada

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## Bhopal: No Silver Linings

I read with interest the article “Lessons Learned? Chemical Plant Safety since Bhopal,” by Ernie Hood (2004). I would recommend it to all interested in safety in chemical plants or safety in other fields.

As mentioned in the article (Hood 2004), this year is the 20th anniversary of the Bhopal tragedy. An international conference on the 20th anniversary of the tragedy, Bhopal and Its Effects on Process Safety, will be held 1–3 December 2004 at the Indian Institute of Technology in Kanpur, India, with a visit to the Bhopal plant planned on 4 December for those who are interested; details are available online (<http://www.iitk.ac.in/infocell/announce/bhopal>). Although the deadline for abstracts has passed, we will still consider outstanding papers.

I would also like to comment on the legend for the figure on page A354 of Hood’s article (Hood 2004): “A toxic cloud’s silver lining?” The question mark does indicate that there are some doubts whether the death of many thousands and the continued suffering of a still larger number should be considered to have a silver lining. In predictable accidents, the large number of deaths produce only untold suffering and not proportionate advantages to the society. The earlier leakages at the Union Carbide Bhopal plant were well known and documented in the newspapers, but neither the company nor the government took enough actions to save the city from the expected accident. According to Charles Perrow of Yale University (Perrow 1999), this is one accident that could not have been worse, contrasting the common cliché “we were lucky it wasn’t worse,” which is used to describe many other accidents and deliberate actions, such as the 9/11 attacks on the World Trade Center (WTC) in New York City. If the explosions in the WTC had taken place later in the day, many more people would have been inside the two towers and many more would have died. No one should say the deaths at the WTC and the

Pentagon provide a silver lining to the war against terrorism. Terrorist acts were already being conducted in several places in Asia, Spain, Northern Ireland, Latin America, and other locations, except the world as a whole decided to look the other way and let individual countries respond. Similarly, because the problems caused by fascism were known or could be foreseen, World War II did not have to happen and cause many millions of deaths. The Allies recently observed the 60th anniversary of the D-Day invasions of several beaches in France; so many deaths and much misery was not necessary for us to understand what fascism could do.

Therefore, I hope that people would reconsider their comments of silver linings on others’ sufferings. The use of the question mark indicates that Hood (2004) was not sure of this, and I commend that hesitant punctuation mark.

*The author declares he has no competing financial interests.*

**J.P. Gupta**

Department of Chemical Engineering  
Indian Institute of Technology  
Kanpur, India  
E-mail: [jpg@iitk.ac.in](mailto:jpg@iitk.ac.in)

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*Editor’s note: The caption referred to by Gupta was written by me, not the author of the article, and I take full responsibility for it. In no way did I intend to trivialize the tragedy at Bhopal. I wanted to make the point that sometimes beneficial lessons may be learned from tragic situations, but my attempt to be “clever” was unfortunate. I regret my choice of wording and that it caused offense.*

**Kimberly Thigpen Tart**

News Editor, *EHP*  
E-mail: [thigpenk@niehs.nih.gov](mailto:thigpenk@niehs.nih.gov)

## Study on Failures to Disclose Conflicts of Interest in Environmental Health Perspectives

The Center for Science in the Public Interest (CSPI) recently investigated conflict of interest disclosures in a cross-section of leading scientific and medical journals, including *EHP*, to determine adherence to their own policies.

*EHP*’s conflict of interest disclosure policy (EHP 2003) outlines a comprehensive

list of “competing financial interests” that an author must disclose along with a published article. They include “grant support, employment (recent, present, or anticipated), ... travel, consultancies, advisory board positions, patent and royalty arrangements, stock shares, ... and the like.” It limits disclosure to situations where an author “may gain or lose financially through publication.” The editors also eschew any effort at enforcement, relying instead on the veracity of authors. *EHP* encourages its readers to scrutinize disclosure statements and offers to publish letters that address alleged inaccuracies.

During the study period of December 2003 through February 2004, *EHP* published 37 scientific studies. Only 2 of the studies indicated they were funded by industry, and only these 2 studies included conflict of interest disclosure statements for at least some of the authors.

The CSPI investigated the first and last authors involved in the 35 studies who did not disclose conflicts of interest. Our investigation revealed at least 3 articles (8.6%) where either the first or last authors should have disclosed conflicts in accordance with the disclosure policy.

First, a Procter and Gamble (P&G) scientist, William Owens, was identified only as a representative of the Organisation for Economic Co-operation and Development. The article (Yamasaki et al. 2003) validated an assay that may be used on P&G products. Owens did not disclose his corporate affiliation in this article, despite having disclosed his P&G employment in a previous *EHP* article (Owens and Koeter 2003).

Second, a Quebec, Canada, group led by Pierre Ayotte of CHUQ-Laval University Medical Center studied the effects of organochlorines and methyl mercury on a remote coastal population (Bilrha et al. 2003). Although there was no disclosure of a conflict of interest, the study was funded in part by the Canadian Network of Toxicology Centers, which is funded in part by the Canadian Chemical Producer Association, an industry trade group. Several of Ayotte’s previous studies were funded in part by the Canadian Chemical Producer Association and the Canadian Chlorine Coordinating Committee, although Ayotte was not directly compensated for this work.

The third group of authors who did not disclose conflicts of interest are scientists at Macquarie University who investigated the sources of lead in children near a zinc-lead smelter (Gulson et al. 2004). Brian Gulson, a professor in Macquarie’s graduate school of the environment, did not disclose that he is listed as an adviser on the website of a consulting group that advised Pasmenco



Ltd. (Laboratory Quality Management Services Pty Ltd. 2003), the company that ran the smelter. In a subsequent e-mail communication, Gulson informed the CSPI that one of his coauthors, Karen Mizon, was the wife of the owner of the consulting group.

In each of those cases, at least one of the authors of a study may gain financially from publication of the article, thus meeting the test of the *EHP* policy. Owens was directly employed by a company that might be affected by his findings. Gulson's colleagues stood to gain financially from a company directly affected by the subject matter of their articles.

Ayotte's study, although a borderline case, should have contained a disclosure statement because he had collaborated on industry-funded studies in the past and the study in question was funded by an industry-supported group. When a field of research is so closely tied to an industry, future funding for research may involve the goodwill of that industry. The spirit of conflict of interest disclosure is best served by full disclosure in such cases.

A fourth case of nondisclosure was not included in our results. In February 2004, *EHP* published a study funded by the National Institutes of Health that claimed polychlorinated biphenyls (PCBs) inhibit a receptor involved in clearing foreign substances from humans (Tabb et al. 2004). One of the authors, Bruce Blumberg, of the Department of Developmental and Cell Biology at the University of California, Irvine, is listed as a co-inventor on a patent granted in 2002 on the gene for an unrelated receptor in frogs. The use claimed for the frog gene is that it may be useful in identifying compounds that affect the receptor.

Should Blumberg disclose that patent as a potential conflict of interest? In an e-mail communication, he defended his failure to disclose by asking, "Do you seriously believe that a patent for a *Xenopus* (frog) nuclear receptor has any bearing on a paper about a mammalian receptor with an entirely different function?" Strict conflict of interest policies would argue "yes," because it is impossible to predict how the information in the new study will affect the use of previous knowledge or what inventions considered irrelevant today may be extremely useful (and lucrative) in the future. Even though *EHP*'s policy (EHP 2003) says "may gain," we did not count his nondisclosure in our statistics.

Judging from the findings of our limited survey, a significant percentage of articles published in *EHP* (8.6%) fail to disclose relevant conflicts of interest of authors. We cannot determine whether authors are not

disclosing the relevant information to *EHP*, or if they are providing the information but *EHP* is not publishing the disclosures. Considering the importance of providing readers with such information, it would seem that *EHP* needs to develop mechanisms to minimize failures to provide "full disclosure of competing financial interests" (EHP 2003). One possible mechanism for improving compliance would be for *EHP* not to accept for 3 years any papers submitted by authors who failed to disclose information about conflicts of interest.

I look forward to your response.

*The author is employed as the director of the Integrity in Science Project at the Center for Science in the Public Interest.*

**Merrill Goozner**

Integrity in Science Project  
Center for Science in the Public Interest  
Washington, DC  
E-mail: mgoozner@cspinet.org

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#### Conflicts of Interest: Owens' Response

To clarify comments from Goozner and the Center for Science in the Public Interest (CSPI), I would like to provide the pertinent facts on my compliance with *EHP*'s policy on competing financial interest disclosure.

First, I was on loan or "seconded" from Procter & Gamble (P&G) to the Organisation for Economic Co-operation and Development (OECD) in Paris. The secondment was arranged at the request of the OECD, and I was officially under contract

and employed by them from October 2002 through October 2003. I offer the former manager of the department, Herman Köeter; the current manager, Andrew Wagner; and their manager, Robert Visser, as references for these points.

Second, in this approximate period, I was a corresponding or contributing author on 11 relevant publications on assays that were either undergoing formal validation at the OECD or were being developed along similar lines for endocrine mechanisms (Ashby et al. 2002a, 2002b, 2003, 2004; Fang et al. 2003; Kanno et al. 2001, 2003a, 2003b; Owens and Ashby 2002; Owens and Köeter 2003; Owens et al. 2003; Yamasaki et al. 2003). In all cases but one, my P&G address was used.

Third, the one exception involved the article questioned by Goozner (Yamasaki et al. 2003). Kanji Yamasaki of the Chemical Evaluation and Research Institute in Japan was the corresponding author in this case. Because work on this manuscript (Yamasaki et al. 2003) occurred while I was at the OECD, Yamasaki used the OECD affiliation when submitting the manuscript to *EHP*. I simply did not notice the affiliation. If I had, I would have changed it to use my P&G affiliation to be consistent with the other 10 publications during this period.

Last, neither I nor P&G have any financial interest in the publications or their subject matter. Rather, this work was done to progress both development and validation work on safety tests that have potential for use to serve a diverse range of parties, including regulators, industry, and the public. Therefore, I do not see how allegations of a competing financial interest are valid in this case, even considering the oversight on the affiliation.

I hope this fully clarifies the record on this matter and lays the CSPI allegations to rest.

*The author is employed by The Procter and Gamble Company.*

**J. William Owens**  
The Procter and Gamble Company  
Central Product Safety  
Cincinnati, Ohio  
E-mail: owens.jw@pg.com

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## Conflicts of Interest: Ayotte's Response

Goozner contacted me by e-mail on 24 June 2004, and I promptly, honestly, and to the best of my knowledge answered questions regarding his claim that I did not disclose a conflict of interest while publishing our article (Bilrha et al. 2003) in *EHP*. Although I thought I made it clear that he was wrong in his allegations, he nevertheless chose to go ahead and include my name in a report published on the Center for Science in the Public Interest's (CSPI) website (CSPI 2004) and in his letter to *EHP*. Here are the facts.

In our 2003 manuscript (Bilrha et al. 2003), we acknowledged funding from the Canadian Network of Toxicology Centers (CNTC). As the corresponding author, I read the conflict of interest statement and indicated that I had nothing to declare, neither for me nor for the coauthors. I did not know at that time that the Canadian Chemical Producer Association was partly funding the CNTC. On their website (CNTC 2004), the CNTC indicates being funded mostly by public sources (90%) and does not mention the identity of private sources. In any case, had I known this at the time of publication, it would not have changed anything, because I never personally received any funds (or compensation of any sort, or stood to gain financially) from the

Canadian Chemical Producer Association or the Canadian Chlorine Coordinating Committee. Goozner is wrong when he mentions that several of my previous studies were funded by these interest groups. I was a coauthor on two articles published previously in *EHP*, in which funding from these interest groups was acknowledged, along with other sources of funding (Sandau et al. 2000, 2002). I collaborated in the work, but I was not the recipient of funds obtained from the Canadian Chemical Producer Association or the Canadian Chlorine Coordinating Committee. Funds from these organizations went to the principal investigator at Carleton University, and not a penny was transferred to me.

I truly believe that the authors of scientific manuscripts should disclose relevant conflicts of interest, and I support enforcing disclosure by appropriate means. However, because Goozner elected to choose the easy way by conducting an Internet-based research, without actually talking to me, he wrongly associated my name with scientific misconduct. I am presently seeking legal advice on this matter.

*The author declares he has no competing financial interests.*

**Pierre Ayotte**

Public Health Research Unit  
CHUQ-Laval University Medical Center  
Quebec, Canada  
E-mail: pierre.ayotte@inspq.qc.ca

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## Conflicts of Interest: Gulson's Response

We commend the Center for Science in the Public Interest (CSPI) for their investigation into conflicts of interest statements in

leading scientific and medical journals, but we take exception to our inclusion (Gulson et al. 2004) as an example of providing misinformation to *EHP*.

Goozner's sweeping statement that my colleague had previously received research funding, compensation, or stood to gain financially from Pasmenco Ltd. is highly inaccurate. We received no research funding, compensation, or financial gain from the company to undertake this study. In fact, if Goozner had read even the abstract of our article, he would have noted that the findings were detrimental to the company, as the dominant source of lead in the environment and children probably derived from smelter emissions. Furthermore, the smelter closed in September 2003 and the company no longer exists. With respect to the association of my colleague, Karen Mizon, to her husband's company and the (consulting) work undertaken for Pasmenco Ltd., the work [an International Organization for Standardization (ISO) Guide 25 accreditation assessment of the company's on-site laboratory (ISO/International Electrotechnical Commission 1990)] was undertaken by the owner for the accreditation body while he was employed by a federal government research organization, and he was not paid for this audit.

*The author declares he has no competing financial interests.*

**Brian Gulson**

Graduate School of the Environment  
Macquarie University  
Sydney, New South Wales, Australia  
E-mail: bgulson@gse.mq.edu.au

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## Conflicts of Interest: Blumberg's Response

In his letter, Goozner suggested that I may have failed to disclose a competing financial interest in regard to an article published in *EHP*. In this article, "Highly Chlorinated PCBs Inhibit the Human Xenobiotic Response Mediated by the Steroid and Xenobiotic Receptor (SXR)" (Tabb et al. 2004), we described differences in how humans and rodents respond to highly chlorinated polychlorinated biphenyls (PCBs).

We concluded that rodents may not be appropriate models for exposure to the class of PCBs discussed in the article and suggested that previous research using rodent models to predict the effects of these PCBs on humans may need to be re-evaluated in light of our findings.

In his letter, Goozner noted that I am the co-inventor of U.S. Patent 6,391,847 ("Method, polypeptides, nucleotide sequence of XOR-6, a vitamin D-like receptor from *Xenopus*"). This patent describes a frog nuclear receptor, now referred to as the benzoate "X" receptor (BXR). As I pointed out on 24 June 2004 in an e-mail message to Goozner, I am not the owner of this patent; the patent is owned and controlled by the Salk Institute for Biological Studies, where I was employed from 1992 to 1998.

It is difficult to understand how Goozner reasons that the frog BXR patent is related in any way to our article on rodent and human SXR (Tabb et al. 2004). My laboratory (Grün et al. 2002) and another laboratory (Moore et al. 2002) have shown that BXR and SXR (also known as PXR) are functionally distinct and that BXR does not function as xenobiotic receptors. Therefore, there is no functional link between BXR and SXR/PXR, as I also pointed out to Goozner in my e-mail.

The *EHP* Instructions to Authors (EHP 2003) defines a competing financial interest thusly: "Competing financial interests may include, but are not limited to, grant support, employment (recent, present, or anticipated), and personal financial interests by the authors, immediate family members, or institutional affiliations that may gain or lose financially through publication." Therefore, for a competing financial interest to exist, there must be at least some realistic probability at the time of submission that publication of the article in *EHP* would lead to financial gain or loss to the authors, their immediate family members, or institutional affiliations. Considering that there is no functional similarity between frog BXR and rodent and human SXR, it is not reasonable to infer that publication of the article regarding the function of SXR in rodents and humans (Tabb et al. 2004) would have any influence on financial interests related to U.S. Patent 6,391,847. Therefore, no potential competing financial interest existed at the time of submission or publication of this manuscript, and as a result, none was disclosed.

In view of these ongoing discussions of interpreting and perhaps heightening the standards regarding disclosure, I wish to inform you of a patent that I just learned was recently issued: U.S. Patent 6,756,491, "Steroid-activated nuclear receptors and

uses therefore" was issued on 29 June 2004, over 4 months after the publication of our article (Tabb et al. 2004) in *EHP*. I am the co-inventor of this patent, which teaches the sequence of SXR and its nucleotide response elements. Because this patent is owned and controlled by the Salk Institute, I was unaware of its status. Had this patent been issued at the time of submission or publication of the article (Tabb et al. 2004) (or had I known that it would issue shortly), I would have disclosed it as a potential competing financial interest. In contrast to the BXR patent, this patent meets the tests described above. It is functionally connected to the subject matter of the article, it clearly has commercial value, and it is foreseeable that I will receive some fraction of whatever income the Salk Institute receives in the course of licensing it to interested parties. Whether or not publication of the article in *EHP* will lead to a financial gain or loss as required by *EHP* policy remains to be seen.

I fully support *EHP*'s competing financial interest policy. Goozner argues in his letter to *EHP*, and in e-mails to me, for a relatively extreme interpretation of what constitutes a competing financial interest, which, as far as I understand it, is beyond the scope of the current *EHP* policy. Whether such an interpretation will become the norm for the scientific community is a matter for future discussion. Although scientists make a good faith effort to comply with disclosure clauses, most are not well trained in understanding the legal nuances involved. It would be very helpful if policies ultimately adopted by journal editorial boards were clearly stated and included appropriate examples so that authors can readily understand the requirements and more effectively comply with the policy.

*The author is the co-inventor of U.S. Patent 6,756,491, "Steroid-activated nuclear receptors and uses therefore," issued on 29 June 2004. This patent is owned and controlled by the Salk Institute for Biological Studies, La Jolla, California, but is likely to generate income to the inventors as a result of licensing.*

#### Bruce Blumberg

Department of Developmental  
and Cell Biology  
University of California, Irvine  
Irvine, California  
E-mail: blumberg@uci.edu

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#### Childhood Leukemia, Military Aviation Facilities, and Population Mixing

In a recent article on the striking cluster of childhood leukemia in 2000-2001 near the Fallon Naval Air Station in Nevada, Steinmaus et al. (2004) referred to the potential relevance of rural-urban population mixing. The population-mixing hypothesis was generated by the observation of excesses of childhood leukemia in two remote and isolated areas in Great Britain that had experienced influxes of significant numbers of workers as a result of the construction and operation of two large nuclear facilities (Kinlen 1988). Such mixing will increase the level of contacts between susceptible (more prevalent in rural areas) and infected individuals, promoting localized (frequently subclinical) epidemics of infections. If childhood leukemia is a rare response to a common—but unidentified—infection, then these localized epidemics will produce excess cases of the unusual complication, childhood leukemia.

Studies of all known examples of extreme rural-urban population mixing in Britain in the past 60 years have, in each instance, revealed significant temporary excesses of childhood leukemia (Kinlen 1995, 2000). These findings have been supported by studies conducted in other countries, most recently by an excess of childhood leukemia in isolated rural counties of the United States where substantial population increases have occurred (Wartenberg et al. 2004). None of these "mixing" situations, however, can compare in intensity with the indirect exposure of the small town of Fallon, Nevada (population 7,536), in only a few years, to over 100,000 military personnel from outside the area receiving training at the naval air station, reaching the extraordinary level of 55,000 in 2000 (GlobalSecurity.org 2003; U.S. Navy 2002). That the world's most sharply defined cluster of childhood leukemia (Alexander 1993; Steinmaus et al. 2004) should occur in association with the most extreme example of rural-urban population mixing could not be more arresting (Kinlen and Doll 2004).

Every opportunity should be taken to investigate the role that infection may have played in this extraordinary cluster of childhood leukemia. Unlike most studies of

marked population mixing, where the relevant circumstances occurred some time ago, this recent cluster provides researchers with the chance to thoroughly study the cases (and other members of the population) for evidence of exposure to the relevant infectious agent. It is an opportunity that should not be missed.

*The author declares he has no competing financial interests.*

**Leo J. Kinlen**

University of Oxford

Radcliffe Infirmary

Oxford, United Kingdom

E-mail: leo.kinlen@dphpc.ox.ac.uk

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*Editor's note: In accordance with journal policy, Steinmaus et al. were asked whether they wanted to respond to this letter, but they chose not to do so.*