Correspondence

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 predominately 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; 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 predominately 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; Lang et al. 1996). This suggests considerable potential for residual confounding.

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 predominately 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; Lang et al. 1996). 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.

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References

Berkowitz GS, Papiernik E. 1993. Epidemiology of preterm birth. Epidemiol Rev 15:441–443.
Ebrahimi SH, Floyd RL, Merritt RK, Decoufle P, Holtzman D. 2000. Trends in pregnancy-related smoking rates in the United States, 1987-1996. JAMA 283:361–366.
Greenland S. 1980. The effect of misclassification in the presence of confounding. Am J Epidemiol 112:564–569.
Holmes RP, Soothill PW. 1996. Intrauterine growth retardation. Crit Opin Obstet Gynecol 8:144–154.
Kramer MS. 1987. Determinants of low birth weight: methodological assessment and meta-analysis. Bull WHO 65:663–737.
Kramer MS. 2003. The epidemiology of adverse pregnancy outcomes: an overview. J Nutr 133:1903–1906S.
Lang JM, Lieberman E, Cohen A. 1996. A comparison of risk factors for preterm labor and term small-for-gestational-age birth. Epidemiology 7:369–376.
Liu K. 1988. Measurement error in its impact on partial correlation and multiple linear regression analysis. Am J Epidemiol 127:864–874.
Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. 2003. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect 111:1773–1778.
Marshall JR, Hastrup JL. 1996. Mismeasurement and the response of strong confounders: uncorrelated errors. Am J Epidemiol 143:1069–1078.
Moore ML. 2003. Preterm labor and birth: what have we learned in the past two decades? J Obstet Gynecol Neonatal Nurs 32:838–849.
Morgenstern H. 1998. Ecological studies. In: Modern Epidemiology (Rothman KJ, Greenland S, eds). Philadelphia: Lippincott-Raven, 499–599.
Nordentoft M, Lou HC, Hansen D, Nim J, Pryd O, Rubin P, et al. 1996. Intrauterine growth retardation and premature delivery: the influence of maternal smoking and psychosocial factors. Am J Public Health 86:347–354.
O’Campo P, Decoufle P, Giovatti F, Decoufle P, Decoufle P. 1990. Smoking cessation interventions for pregnant women: review and future directions. Semin Perinatol 14:279–285.
Petridou E, Panagiotopoulou K, Katsayanni K, Sapanos E, Trichopoulos D. 1990. Tobacco smoking, pregnancy estrogens, and birth weight. Epidemiology 1:247–250.
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 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 (Dudevok 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.
socioeconomic status, and mortality in Vancouver, Canada. J Expo Anal Environ Epidemiol 13:427–435.

Wang X, Ding H, Ryan L, Xu X. 1997. Association between air pollution and low birth weight: a community-based study. Environ Health Perspect 105:514–520.

Xu X, Ding H, Wang X. 1995. Acute effects of total suspended particulate and sulfur disoxides on preterm delivery: a community-based cohort study: Arch Environ Health 50:407–415.

Yang D, Chen Y, Shi Y, Burnett RT, McGrail K, Krewski D. 2003. Association between ozone and respiratory admissions among children and the elderly in Vancouver, Canada. Inhal Toxicol 15:1297–1308.

Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, et al. 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ Health Perspect 108:419–426.

**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/infolcell/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 cliche “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.

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**REFERENCES**

Hood E. 2004. Lessons learned? Chemical plant safety since Bhopal. Environ Health Perspect 112:A352–A359.

Perrow C. 1999. Normal Accidents. Princeton, NJ:Princeton University Press.

**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.

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**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 Köeter 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 Pasminco...
The author is employed by the Procter and Gamble Company.

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Conclusions

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References

Ashby J, Lefevre PA, Timwell H, Odum J, Owens W. 2004. Testosterone-stimulated weaning rats as a replacement for castrated rats in the Hershberger anti-androgen assay. Regul Toxicol Pharmacol 39:229–238.

Ashby J, Owens W, Dehghengh R, Odum J. 2002a. Concept evaluation: an assay for receptor-mediated and biochemical antiestrogens using pubertal rats. Regul Toxicol Pharmacol 35:393–397.

Ashby J, Owens W, Lefevre PA. 2002b. Concept evaluation: androgen-stimulated immature intact male rats as an assay for antiandrogens. Regul Toxicol Pharmacol 35:280–285.
Correspondence

Yamasaki K, Sawaki M, Ohta R, Okuda H, Katayama S, Owens W, Ashby J, Odum J, Onyon L. 2003. The OECD program to validate the rat uterotrophic bioassay. Phase 2: coded single dose studies. Environ Health Perspect 111:1550–1558.

Kanno J, Onyon L, Peddada S, Ashby J, Jacob E, Owens W. 2003. The OECD program to validate the rat uterotrophic bioassay. Phase 2: dose–response studies. Environ Health Perspect 111:1530–1549.

Owens JW, Ashby J. 2002. Critical review and evaluation of the uterotrophic bioassay for the identification of possi-
ble estrogen agonists and antagonists: in support of the validation of the OECD uterotrophic protocols for the lab-
oratory rodent. CRC Crit Rev Toxicol 32:445–520.

Owens W, Köster HBMW. 2003. The OECD special program to validate the rat uterotrophic bioassay: an overview. Environ Health Perspect 111:1527–1529.

Owens W, Ashby J, Oudin J, Onyon L. 2003. The OECD program to validate the rat uterotrophic bioassay. Phase 2: dietary phytoestrogen analyses. Environ Health Perspect 111:1559–1567.

Yamazaki K, Kiyosawa M, Dhta R, Okuda H, Katayama S, Yamada T, et al. 2003. OECD validation of the Hershberger assay in Japan: phase 2 dose response of methyltesto-
terone, vinclozolin, and p,p’-DDE. Environ Health Perspect 111:1912–1919.

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, nei-
ther 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 leading scientific and medical journals, but we take exception to our inclusion (Gulson et al. 2004) as an example of providing mis-
information to EHP.

Goozner’s sweeping statement that my colleague had previously received research funding, compensation, or stood to gain financially from Pasminco 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 environ-
ment and children probably derived from smelter emissions. Furthermore, the smelter closed in September 2003 and the company no longer exists. With respect to the associ-
ation of my colleague, Karen Mizon, to her husband’s company and the (consulting) work undertaken for Pasminco Ltd., the work [an International Organization for Standardization (ISO) Guide 25 accredita-
tion assessment of the company’s on-site lab-
oratory (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.

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REFERENCES

Bilrha H, Roy R, Moreau B, Belles-Iles M, Devaillly E, Ayotte P. 2003. In vitro activation of cord blood mononuclear cells and cytokine production in a remote coastal population exposed to organochlorines and methyl mercury. Environ Health Perspect 111:1952–1957.

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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 chlo-

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REFERENCE

Gulson BL, Mizon KJ, Davis JD, Palmer JM, Vimpani G. 2004. Identification of sources of lead in children in a primary zinc–lead smelter environment. Environ Health Perspect 112:52–60.

ISO/International Electrotechnical Commission. 1990. ISO Guide 25: General Requirements for the Competence of Calibration and Testing Laboratories. 3rd ed. Geneva: International Organization for Standardization.

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information to EHP.
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, 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 BXRs do 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.

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REFERENCES

EHP. 2003. Instructions to authors. Available: http://ehp.niehs.nih.gov/docs/admin/edpolicy.html [accessed 12 December 2003].

Grün F, Venkatesan RN, Tabb MM, Zhou C, Cao J, Hemmati D, et al. 2002. Benzoate X receptors α and β are pharmacologically distinct and do not function as xenobiotic receptors. J Biol Chem 277:43891–43897.

Moore LB, Magilch JM, McKee DD, Wisely B, Wilson TM, Kliewer SA, et al. 2002. Pregnen X receptor (PXR), constitutive androstane receptor (CAR), and benzoate X receptor (BXR) define three pharmacologically distinct classes of nuclear receptors. Mol Endocrinol 16:977–986.

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 would 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.

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REFERENCES

Alexander FE. 1993 Viruses, clusters and clustering of childhood leukaemia: a new perspective? Eur J Cancer 29A:1423–1424.

GlobalSecurity.org. 2003. Naval Air Station Fallon. Available: http://www.globalsecurity.org/military/facility/fallon.htm [accessed 5 April 2004].

Kinlen L. 1988. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. Lancet 2:1323–1327.

Kinlen LJ. 1995. Epidemiological evidence for an infective basis in childhood leukaemia. Br J Cancer 71:1–5.

Kinlen LJ. 2000 Infection, childhood leukaemia and the Seascalke cluster. Radio Prot Bull 228:9–18.

Kinlen L, Doll R. 2004. Population mixing and childhood leukaemia: Fallon and other US clusters [Editorial]. Br J Cancer 91:1–3.

Steinmaus C, Lu M, Todd RL, Smith AH. 2004. Probability estimates for the unique childhood leukemia cluster in Fallon, Nevada, and risks near other U.S. military aviation facilities. Environ Health Perspect 112:766–771.

U.S. Navy 2002. Naval Air Station, Fallon, Nevada. History. Available: http://www.fallon.navy.mil/history.htm [accessed 12 May 2004].

Wartenberg D, Schneider D, Brown S. 2004. Childhood leukemia incidence and the population mixing hypothesis in US SEER data. Br J Cancer 90:1771–1776.

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.