The correspondence section is a public forum and, as such, is not peer-reviewed. EHP *is not responsible for the accuracy, currency, or reliability of personal opinion expressed herein; it is the sole responsibility of the authors.* EHP *neither endorses nor disputes their published commentary.*

Phosphine Toxicity: Ethical Questions

In their article McDaniel et al. (2005) presented three case studies, one involving an evaluation by Sciences International, Inc. (Pepelko et al. 2004), of which I am the president and CEO. This case study was related to the reregistration of phosphine by the U.S. Environmental Protection Agency (EPA). McDaniel et al. (2005) make two principal accusations: *a*) that I improperly used my status as editor-in-chief of *Risk Analysis: An International Journal* (*Risk Analysis*) in the publication of an article on phosphine toxicity, and *b*) that work done by Sciences International led the U.S. EPA to make an improper decision about phosphine risk. There are serious misrepresentations and omissions in this article. Also, neither the authors nor *EHP* contacted me before posting of the article.

Sciences International was engaged in 1998 by a coalition of companies with an interest in the fumigation uses of phosphine to provide an evaluation of phosphine acute toxicity for consideration in the U.S. EPA phosphine reregistration process. The membership of the coalition was diverse, representing industries in food processing, grain milling, rail transportation, and tobacco.

Based on this work, an article was published by scientists at my firm in 2004 on the toxicity of phosphine in *Risk Analysis* (Pepelko et al. 2004). The article was published 5 years after the U.S. EPA made their decision (U.S. EPA 2001) and presented a somewhat more conservative conclusion than that presented by the U.S. EPA. Quite contrary to the impression given by McDaniel et al. (2005), this article went through a thorough peer review and was handled properly in all respects. As a matter of policy, when I, or any member of the editorial staff for *Risk Analysis,* have a potential conflict of interest, we recuse ourselves from the review. Therefore, to avoid any conflict of interest, I asked Curtis Travis, the editor-in-chief emeritus of *Risk Analysis,* to handle the review of the two articles that were submitted in 2002, after the reregistration decision for phosphine. Travis sent the draft articles to independent reviewers and ultimately rejected both articles. His comments included the recommendation to consolidate them into one article. We submitted a revised and consolidated article in 2003, again handled by Travis; the article was accepted and published in October 2004 (Pepelko et al. 2004). McDaniel et al. (2005) made an issue of a suggestion I made that the article (Pepelko et al. 2004) could be expedited in the publication process. It is not uncommon for journals to expedite articles that are of timely interest, such as being relevant to a current decision and particularly in cases of new scientific developments. However, the phosphine article (Pepelko et al. 2004) was ultimately never expedited, a fact that McDaniel et al. did not mention after making the initial accusation. Our article (Pepelko et al. 2004) was handled properly and professionally in all respects.

Secondly, McDaniel et al. (2005) implied that the U.S. EPA improperly selected its uncertainty factors for the phosphine risk assessment based on the analysis done by Sciences International. McDaniel et al. did little to make the case that the U.S. EPA's decision was improper, other than to point out that not everyone agreed about it. It is notable that our article (Pepelko et al. 2004) recommended an exposure standard of 0.1 ppm, which is lower (more stringent) than the U.S. EPA's earlier decision (U.S. EPA 2001), and also lower than the standards set by the American Conference of Governmental Industrial Hygienists (ACGIH 2000), the Occupational Safety and Health Administration (OSHA 1999), and the National Institute for Occupational Safety and Health (NIOSH 1997). As described above, our article went through a rigorous peer review and represents a significant scientific contribution; slight scientific differences are not unusual, given the uncertainties involved in setting acute toxicity standards.

McDaniel et al. (2005) provided little description of the ultimate regulatory decision made by the U.S. EPA in regard to phosphine (U.S. EPA 2001), which is necessary to provide context to this discussion. The changes made to phosphine usage were significant, including the requirement for site-specific fumigant management plans, training and certification requirements, and additional label modifications to reduce harmful exposures. These changes represent a significant change in how phosphine is used, substantial requirements and burdens for users, and significant public health protections.

There are legitimate scientific issues that require resolution for setting safe acute toxicity levels, for example, for substances of interest for homeland security. Differing durations of exposure and the accompanying severity of effects present a challenge for evaluating health effects associated with short-term, acute exposures. Investigative tools, including the use of categorical regression and the regional gas-dose model for extrapolating from rat inhalation studies to humans, have been explored by the U.S. EPA and Sciences International for their utility in defining safe acute toxicity levels (U.S. EPA 1994, 2000); the applications of these approaches have been investigated for their utility in setting acute toxicity standards for phosphine. McDaniel et al. (2005) did not attempt to address these challenging scientific issues.

McDaniel et al. (2005) made no attempt to further scientific knowledge; therefore, their article appears to fall short of the scientific standards of *EHP*.

The author is the president and chief executive officer of Sciences International, Inc., which provides services to clients in the public and private sectors and trade associations; she has received funding from the Phosphine Coalition for previous work but received no financial support for writing this letter.

Elizabeth L. Anderson
Risk Analysis: An International Journal
Alexandria, Virginia
E-mail: elanderson@sciences.com

References

ACGIH. 2000. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH:American Conference of Governmental Industrial Hygienists.

McDaniel PA, Solomon G, Malone RE. 2005. The tobacco industry and pesticide regulations: case studies from tobacco industry archives. Environ Health Perspect 113:1659–1665; doi:10.1289/ehp.7452 [Online 8 August 2005].

NIOSH. 1997. Pocket Guide to Chemical Hazards. Washington, DC:National Institute for Occupational Safety and Health.

OSHA. 1999. Health Effects Discussion and Determination of Final PEL. Washington, DC:Occupational Safety and Health Administration.

Pepelko B, Seckar J, Harp PR, Kim JH, Gray D, Anderson EL. 2004. Worker exposure standard for phosphine gas. Risk Anal 24(5):1201–1213.

U.S. EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90-066F. Washington, DC:U.S. Environmental Protection Agency, Office of Health and Environmental Assessment.

U.S. EPA. 2000. CatReg Software Documentation. EPA/600/R-98/053F. Washington, DC:U.S. Environmental Protection Agency, Office of Research and Development.

U.S. EPA. 2001. Amendment to Reregistration Eligibility Decision for Aluminum Phosphide and Magnesium Phosphide; Notice of Availablity. Fed Reg 66:8790–8792.

Phosphine Toxicity: McDaniel et al. Respond

We appreciate the opportunity to respond to Anderson's letter. We do thank Anderson for providing details on the review process for the article eventually published in *Risk Analysis* (Pepelko et al. 2004) that was based on Sciences International's work for the Phosphine Coalition. In our article (McDaniel et al. 2005), we did not accuse Anderson of improperly using her status as editor-in-chief of the journal in the publication process.

Instead, we point out that she suggested—in a 1999 memorandum to Phosphine Coalition member Joel Seckar—that the peer-review process for the paper could be expedited (Anderson 1999). We then pointed out that the article was ultimately published in 2004. We did not conclude from this that the paper was improperly handled. Indeed, we assumed that it was not, given the 5-year delay between the 1999 proposal and the 2004 publication date. Anderson notes that "it is not uncommon for journals to expedite articles that are of timely interest." However, we would question whether it is or should be accepted practice for editors who are also authors to initiate an expedited process for their own papers, or to suggest that they would be willing to do so in order to advance the interests of a regulated industry that has hired them in the context of regulatory deliberations.

In addition, we did not state in our article (McDaniel et al. 2005) that the work done by Sciences International led the U.S. Environmental Protection Agency (EPA) to make an improper decision about phosphine risk. We stated that the Phosphine Coalition hired Sciences International to write a report challenging the scientific basis of the U.S. EPA's proposed risk mitigation measures, focusing on reducing or eliminating the interspecies uncertainty factor that led to the U.S. EPA's proposed exposure level of 0.03 ppm (Seckar 1999). Sciences International did so; we offered evidence to show that *a*) an early draft was deemed too uncertain and tentative by members of the Phosphine Coalition and was revised by Sciences International to strengthen the language; *b*) the interim report submitted by Sciences International to the U.S. EPA was judged in a memorandum by a U.S. EPA toxicologist (Barolo 1999; Sciences International 1999a, 1999b) to lack the human data necessary to justify eliminating the interspecies uncertainty factor (Whalan 1999); *c*) the U.S. EPA made its final decision on the risk mitigation measures in December 1999, before receiving the final revised report from Sciences International (Sharp 1999). The conclusion we drew from this evidence, which we believe is reasonable regardless of the outcome of the decision itself, is that the U.S. EPA's regulatory decision making needs to be more transparent. If the U.S. EPA had provided us with the additional internal documents we requested, we might have been able to better understand how the agency made its final regulatory decision, one that left the existing worker exposure standard in place and failed to add community buffer zones and notification requirements as originally proposed.

Anderson suggests that, in our article (McDaniel et al. 2005), we should have examined such challenging scientific issues as categorical regression and the regional gas-dose model for extrapolating from rat inhalation studies to humans. This was not the focus of our work. We examined cases in which the tobacco industry intervened to influence aspects of the pesticide regulatory process. In the case of phosphine, our focus was on the proposed risk mitigation measures that were deemed of primary concern for the tobacco industry: the more stringent worker exposure standard, the buffer zone, and the notification requirements. All of these public health protections were adamantly opposed by the industry coalition, and none of them survived in the final regulatory decision.

We regret that Anderson attacks *EHP* in responding to our article (McDaniel et al. 2005). Our work underwent several levels of peer review before its publication; obviously, we believe that it advances knowledge regarding important regulatory processes—processes that, for good or ill, are both sociopolitical and scientific as they unfold, and in which we believe many *EHP* readers have interest. As we pointed out in our conclusion, although others have charged that agencies responsible for protecting human health and the environment are unduly influenced by the industries they regulate, it is rare to be able to study this process from the perspective of the regulated industry. The tobacco industry documents provide a unique opportunity to identify tactics that industry applies to a regulatory agency when trying to influence the outcome of a decision. The fact that these documents were prepared at a time when their eventual public disclosure was not anticipated raises their archival evidentiary value above what might be learned from contemporaneous interviews years later with persons whose economic interests were at stake in the events discussed. We stand by our interpretation of the documentary record.

P.A.M. and R.E.M. declare they have no competing financial interests. G.S. is employed by the Natural Resources Defense Council, an environmental nonprofit organization with an interest in ensuring that regulations of toxic chemicals are as health-protective as feasible.

Patricia A. McDaniel
Center for Tobacco Control Research and Education
University of California
San Francisco, California
E-mail: patricia.mcdaniel@ucsf.edu

Gina Solomon
Natural Resources Defense Council
San Francisco, California

Ruth E. Malone
Department of Social and Behavioral Sciences & School of Nursing
University of California
San Francisco, California

References

Anderson E. 1999. Recommended Plan for EPA Meeting Follow-Up. R.J. Reynolds. Bates No. 521558671. Available: http://legacy.library.ucsf.edu/tid/trx60d00 [accessed 13 April 2004].

Barolo D. 1999. Interim Status Report: Toxicity Review of Phosphine Reply, 28 June. RJ Reynolds. Bates No. 521558670. Available: http://legacy.library.ucsf.edu/tid/srx60d00 [accessed 13 April 2004].

McDaniel PA, Solomon G, Malone RE. 2005. The tobacco industry and pesticide regulations: case studies from tobacco industry archives. Environ Health Perspect 113:1659–1665; doi:10.1289/ehp.7452 [Online 8 August 2005].

Pepelko B, Seckar J, Harp PR, Kim JH, Gray D, Anderson EL. 2004. Worker exposure standard for phosphine gas. Risk Anal 24(5):1201–1213.

Sciences International. 1999a. Interim Status Report: Toxicity Review of Phosphine, 22 June. RJ Reynolds. Bates No. 521558656/521558664. Available: http://legacy.library.ucsf.edu/tid/orx60d00 [accessed 15 June 2004].

Sciences International. 1999b. Interim Status Report: Phosphine Toxicity Review, July. RJ Reynolds. Bates No. 521576948/521576955. Available: http://legacy.library.ucsf.edu/tid/fic70d00 [accessed 13 April 2004].

Seckar J. 1999. Phosphine Risk Mitigation Measures Financial Support Science Issues, 22 June. RJ Reynolds. Bates No. 521558565/521558566. Available: http://legacy.library.ucsf.edu/tid/lrx60d00 [accessed 16 June 2004].

Sharp A. 1999. Latest Status of RMMs. RJ Reynolds. Bates No. 521597382/521597383. Available: http://legacy.library.ucsf.edu/tid/gmy20d00 [accessed 13 April 2004].

Whalan JE. 1999. Memorandum from J Whalan, Health Effects Division, U.S. Environmental Protection Agency, to M Hartman, Reregistration Division. Phosphine Gas: Response to Comments from the Phosphine Coalition. 12 August. [13 November 2003 U.S. EPA FOIA request].

Effects of Lead on IQ in Children

Lanphear et al. (2005) pooled data from seven prospective studies that had been initiated to test the effect of prenatal and early childhood lead exposure. The primary investigators of these studies had planned the studies so that the sequence of data collection might shed light on the question of early causation. At that time, most of us anticipated a strong association of prenatal exposure and developmental deficit related to rapid prenatal central nervous system (CNS) development (Ernhart 1992). Lanphear et al. (2005) pooled our data to report a significant association of cord blood lead (BPb) and IQ (intelligence quotient) and concluded that prevention of lead exposure must occur before pregnancy or childbirth. Their analysis did not include control of the sociodemographic factors known to confound research on the topic; hence, the conclusion is not justified.

In the balance of the report, Lanphear et al. (2005) selected concurrent lead level at 5–6 years of age, as opposed to earlier measures of lead exposure, because it had the highest association with IQ. The closer association for the lead measurement made at or near the time of the IQ test may reflect concomitant factors not well controlled in the analyses. In most studies, parental intelligence and HOME (Home Observation for Measurement of the Environment; a measure

of caretaking and parental stimulation) are major predictors of child IQ. These variables are difficult to measure (Kaufman 2001), and undercontrol of confounding is likely. Bias is particularly likely in the data of the Rochester, New York, cohort (Canfield et al. 2003) because the HOME (toddler version) was administered at the age of 2 years, not at 5–6 years of age.

Using available covariate data, Lanphear et al. (2005) did report a deficit of approximately 2 IQ points for the BPb range of 10–20 μg/dL. This replicates previous analyses conducted by Pocock et al. (1994). The latter investigators interpreted the association as possibly due to limited control of confounding, selection biases, and/or reverse causality.

The most problematic portion of the article by Lanphear et al. (2005) concerns very low lead exposure. The authors selected data for the 244 children who had peak, or maximal, BPb levels < 10 μg/dL. The decline in IQ for this group consisted of 6.2 points for the concurrent BPb range of 1–10 μg/dL ($\beta = -0.80$, SE = 0.48, $p = 0.09$). For a more restricted group of 103 children with peak BPb levels < 7.5 μg/dL, the association was stronger ($\beta = -2.94$, SE = 1.14, $p = 0.012$) although the sample size was further truncated. Lanphear et al. (2005) concluded that "lead exposure in children who have maximal BPb levels < 7.5 μg/dL is associated with intellectual deficits." There are major problems with this conclusion.

First, groups selected on the basis of peak lead level < 10 μg/dL and < 7.5 μg/dL differed significantly from the balance of the sample on factors omitted as noncontributing for the full study. Lanphear et al. (2005) ignored race (U.S. cohorts), maternal age, and maternal use of cigarettes and alcohol during pregnancy in the analyses of these groups.

Second, cohort contribution was critical for these groups. Of the 103 children with BPb levels < 7.5 μg/dL (Lanphear et al 2005), 67% were from the Rochester cohort. In addition to the limitation in the HOME data, information regarding this cohort at 3 and 5 years of age reflects peculiar shifts in demographic variables, including race and maternal education (Canfield et al. 2003; Canfield RL, Henderson CR, Lanphear BP, Cory-Schlecta DA, Smith EG, Cox C, unpublished data). This was a prospective study, yet the sample increased from 154 children at 5 years of age to 182 at 6 years of age, and the number with peak lead levels < 10 μg/dL increased from 86 to 103. Canfield et al.'s 6-year data used in the pooled analysis have not been published, and my requests for further information were denied.

Finally, there was no significant association of IQ and three of the four indices of lead exposure—early childhood, peak (or maximal), and lifetime average—for the segments of the sample with peak lead levels < 10 μg/dL or < 7.5 μg/dL. Lanphear et al. (2005) omitted these analyses from their article.

Lanphear et al. (2005) reached conclusions intended to support policies to further reduce the already low level of childhood lead exposure. Although I contributed data [the Cleveland Study (Ernhart et al. 1989)] and participated in planning and review of analyses, I withdrew from authorship because I could not concur with the manuscript, including the inferences drawn.

The author declares she has no competing financial interests.

Claire B. Ernhart
Case Western Reserve University
Strongsville, Ohio
E-mail: cxe@po.cwru.edu

References

Canfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. 2003. Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. N Eng J Med 348:1517–1526.

Ernhart CB. 1992. A critical review of low-level prenatal lead exposure in the human: 2. Effects on the developing child. Reprod Toxicol 6:21–40.

Ernhart CB, Morrow-Tlucak M, Wolf AW, Super D. Drotar D. 1989. Low-level lead exposure in the prenatal and early preschool periods: intelligence prior to school entry. Neurotoxicol Teratol 11:161–170.

Kaufman AS. 2001. Do low levels of lead produce IQ loss in children? A careful examination of the literature. Arch Clin Neuropsych 16:303–341.

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger D, et al. 2005 Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect 113: 894–899; doi:10.1289/ehp.7688 [Online 18 March 2005]

Pocock SJ, Smith M, Baghurst PA. 1994 Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. BMJ 309:1189–1197.

Lead and IQ in Children: Lanphear et al. Respond

As described in our original article (Lanphear et al. 2005), we decided *a priori* to focus our analyses on the blood lead (BPb) variable that had the strongest association with IQ (intelligence quotient) scores. This decision was made to limit the number of analyses and to minimize problems with multiple comparisons. There was a clear consensus among the co-investigators—which originally included Ernhart—to use this strategy. Because concurrent BPb concentration was the strongest predictor of intellectual functioning, we focused most of our analyses on this variable.

There are now several studies indicating that concurrent or lifetime average BPb concentration are better predictors of children's IQ scores than measures taken in early childhood (Baghurst et al. 1992; Canfield et al. 2003; Chen et al. 2005; Dietrich et al. 1993; Tong et al. 1996; Wasserman et al. 2003). Thus, existing evidence indicates that interpretation of this literature should rely on concurrent or lifetime measures of BPb concentration.

Ernhart is concerned that we found no significant association of IQ and three of the four indices of lead exposure at peak BPb levels < 10 μg/dL or < 7.5 μg/dL (Lanphear et al. 2005). In addition to a significant inverse association of concurrent BPb concentration and IQ score for children with maximal BPb levels < 7.5 μg/dL, we found a consistent inverse association for lifetime average BPb concentration ($\beta = -3.13$, $p = 0.054$). As we reported, the relationship of peak BPb concentration and early childhood BPb concentration was not as predictive of children's IQ scores.

Ernhart is particularly concerned about our analyses for children with "very low" lead exposure (Lanphear et al. 2005). The results of our parsimonious analysis for children who had maximal BPb concentrations < 10 μg/dL and < 7.5 μg/dL were entirely consistent with the fully adjusted model. When we included all of the additional covariates, concurrent BPb concentration changed by < 5%, and it remained statistically significant ($\beta = -2.99$, $p = 0.019$) for the children with maximal BPb levels < 7.5 μg/dL. When we further restricted the analysis to U.S. cohorts and introduced race as a covariate, race was clearly not a significant factor, and the pattern remained similar. These secondary analyses support our original conclusion that there is an inverse relationship of lead exposure and intellectual function, with greater decrements at lower BPb concentrations (Lanphear et al. 2005).

We agree that using an early measure of the HOME (Home Observation for Measurement of the Environment) inventory (Caldwell and Bradley 1984) in the Rochester cohort was a potential limitation. Still, when we excluded the Rochester cohort from the pooled analysis, the coefficient changed by < 3% and remained statistically significant (Lanphear et al. 2005). Thus, this limitation did not alter the conclusions of the study.

Ernhart is critical about the "peculiar" increase in sample size and shifts in demographic variables in the Rochester study. Although some families became "too busy" to participate when their children were toddlers, we routinely invited them to participate in subsequent visits. A larger number of families were willing to return for an evaluation as their children aged.

We conducted a secondary analysis of studies that included prenatal BPb concentration. Contrary to Ernhart's comment,

prenatal lead exposure was not significantly associated with children's IQ scores in adjusted analyses (Lanphear et al. 2005). We concluded that "prevention of lead exposure must occur before pregnancy or a child's birth" (Lanphear et al. 2005) because children are particularly vulnerable to lead intake and absorption during the first 2–3 years of life (Clark et al. 1985; Lanphear et al. 2002; Ziegler et al. 1978).

Ernhart argues that her request for further information about the 6-year data from the Rochester study "was denied." The earlier measures of intellectual function in the Rochester children (i.e., at 3 and 5 years of age) were measured using the Stanford Binet test (Canfield et al. 2003). The IQ test at 6 years of age, which was measured using the Wechsler Preschool and Primary Scales of Intelligence, was done specifically for the pooled analysis. We believed that it was in the best interest of public health to confirm the findings of the original Rochester study with the larger pooled analysis rather than await publication of the follow-up 6-year IQ tests.

Numerous studies have found evidence for adverse consequences of childhood lead exposure at BPb levels < 10 μg/dL (Bellinger and Needleman 2003; Chiodo et al. 2004; Fulton et al. 1987; Lanphear 2000; Sood et al. 2001; Walkowiak et al. 1998; Wasserman et al. 2000). These studies provide sufficient evidence that childhood lead exposure should be reduced even more by banning all nonessential uses of lead and further reducing the allowable levels of lead in air emissions, house dust, soil, water, and consumer products.

The authors declare they have no competing financial interests.

Bruce P. Lanphear
Richard Hornung
Jane Khoury
Kimberly Yolton
Kim N. Dietrich
Departments of Pediatrics and of Environmental Health
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
E-mail: bruce.lanphear@chmcc.org

References

Baghurst PA, McMichael AJ, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ, et al. 1992. Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study. N Engl J Med 327:1279–1284.

Bellinger DC, Needleman HL. 2003. Intellectual impairment and blood lead levels. N Engl J Med 349:500–502.

Caldwell BM, Bradley RR. 1984. Home Observation for the Measured Environment. Little Rock, AR:University of Arkansas at Little Rock.

Canfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. 2003. Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. N Engl J Med 348:1517–1526.

Chen A, Dietrich KN, Ware JH, Radcliffe J, Rogan WJ. 2005. IQ and blood lead from 2 to 7 years of age: are the effects in older children the residual of high blood lead concentrations in 2-year-olds? Environ Health Perspect 113:597–601.

Chiodo LM, Jacobson SW, Jacobson JL. 2004. Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol Teratol 26:359–371.

Clark CS, Bornschein RL, Succop P, Que Hee SS, Hammond PB, Peace B. 1985. Condition and type of housing as an indicator of potential environmental lead exposure and pediatric blood lead levels. Environ Res 38:46–53.

Dietrich KN, Berger OG, Succop PA, Hammond PB, Bornschein RL. 1993. The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school entry. Neurotoxicol Teratol 15:37–44.

Fulton M, Raab G, Thomson G, Laxen D, Hunter R, Hepburn W. 1987. Influence of blood lead on the ability and attainment of children in Edinburgh. Lancet 1:1221–1226.

Harrell F. 2001. Regression Modeling Strategies. New York:Springer Verlag.

Lanphear BP, Dietrich K, Auinger P, Cox C. 2000. Cognitive deficits associated with blood lead levels <10 μg/dl in US children and adolescents. Public Health Rep 115:521–529.

Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. 2002. Environmental lead exposure during early childhood. J Pediatr 140:40–47.

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al. 2005. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect 113:894–899.

Sood B, Delaney-Black V, Covington C, Nordstrom-Klee B, Ager J, Templin T, et al. 2001. Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect. Pediatrics 108(2):E34. Available: http://pediatrics.aappublications.org/cgi/content/full/108/2/e34 [accessed 1 December 2005].

Tong S, Baghurst P, McMichael A, Sawyer M, Mudge J. 1996. Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study. BMJ 312:1569–1575.

Walkowiak J, Altmann L, Kramer U, Sveinsson K, Turfeld M, Weishoff Houben M, et al. 1998. Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing. Neurotoxicol Teratol 20:511–521.

Wasserman GA, Factor-Litvak P, Liu X, Todd AC, Kline JK Slavkovich V, et al. (2003) The relationship between blood lead, bone lead and child intelligence. Neuropsychol Dev Cogn C Child Neuropsychol 9:22–34.

Ziegler EE, Edwards BB, Jensen RI, Mahaffey KR, Fomon SJ. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29–34.

Sheep Reared on Sewage Sludge–Treated Pasture: Flawed Conclusions

I read the article by Paul et al. (2005) with interest. Although the authors devoted considerable energy and resources to their study, I believe that the experimental design is fundamentally flawed and the authors' conclusions are not supported by the facts. The flaw in this grazing experiment is that the control treatment, a pasture not treated with sewage sludge, is not a valid control. A valid experimental control should be as close to identical to the treatment(s) as possible, except for the factor under investigation.

In the study of Paul et al. (2005), the pastures received 250 kg nitrogen/ha from sewage sludge or from mineral fertilizer. Under the climatic conditions of the experiment, the sludge nitrogen would be equivalent to about 70 kg nitrogen from mineral fertilizer, with much of the rest of the nitrogen (and carbon) going into soil organic matter stocks. Thus, the "control" received three times as much plant-available nitrogen as the sludge pasture, and the herbage yield would have been greater. The lower herbage yield and more restricted diet on the sludge plot is borne out by the lighter weights of the ewes and the fetuses.

In addition to the difference in nitrogen, there was almost certainly a difference in the phosphorus supply. Paul et al. (2005) did not describe fertilizer applications apart from nitrogen, but I doubt that they added as much phosphorus to the control plot as they did to the treated plot in the form of sludge content. There is also the question of the other nutrients that would have been added in the sludge (potassium, magnesium, sulfur, calcium, and minor nutrients).

The lesser amount of available nitrogen and the much greater phosphorus (and the other nutrients) over ≥ 7 years would have almost certainly changed the sward composition. For example, there would almost certainly be much more clover in the sludge plots. Clover and other legumes are rich in phytoestrogens; therefore, if the effects observed by Paul et al. (2005) were due to endocrine-active substances in the diet, these substances could well have been phytoestrogens.

Paul et al. (2005) noted that some authors have reported similar effects in sheep on restricted diets, but other authors have not found the effects; therefore, this appears inconclusive. Paul et al. (2005) found physiologic effects but did not prove causation.

From the results of Paul et al. (2005), one could conclude that mineral nitrogen increased the number of quadruplets (which is bad from a farmer's point of view because the ewe does not have enough milk for four lambs) and sludge gave consistently more triplets (good for farmers), but that would not be accurate. Based on their data, one could also say that statistically significantly more ewes escape from mineral nitrogen–fertilized fields than from sludge-treated ones, but that would be silly.

The diets of the two populations were different because the pastures were managed differently and, as a consequence, the animals responded differently; it would not be valid to say more.

The author declares he has no competing financial interests.

Tim Evans
Tim Evans Environment
Ashtead, Surrey, England
E-mail: tim@timevansenvironment.com

Reference

Paul C, Rhind SM, Kyle CE, Scott H, McKinnell C, Sharpe RM. 2005. Cellular and hormonal disruption of fetal testis development in sheep reared on pasture treated with sewage sludge. Environ Health Perspect 113:1580–1587; doi:10.1289/ehp.8028 [Online 11 July 2005].

Sheep Reared on Sewage Sludge–Treated Pasture: Sharpe Responds

We thank Evans for his interest in our article (Paul et al. 2005) and for his comments. He appears to have misunderstood the purpose of our study, which was to provide evidence as to whether or not the complex mixture of chemicals that are present in treated sewage sludge are able to exert any effects on the developing fetal testis in the sheep. This information might provide insights into current understanding about the impact of environmental chemicals on development and malfunction of the human testis. In this study we chose what we considered to be the most appropriate control treatment, which was to maintain pasture in its normal format according to local environmental conditions with the addition of appropriate amounts of inorganic nitrogenous fertilizer. The aim was not to control exactly for the relative amounts of all other organic and/or inorganic materials because this would be almost impossible to do when considering the complex makeup of sewage sludge.

Possible differential effects of the control and sewage sludge treatment on growth of the sward in the two pastures and their consequent contribution to different nutritional effects in the ewes maintained on that pasture were controlled by varying the stocking levels according to the sward length. This was clearly indicated in the "Materials and Methods" of our article (Paul et al. 2005). Evidence that this approach was successful can be gleaned from the observation that there was no difference in body weight between the pregnant ewes maintained on the two types of pasture. Evans must have misunderstood our article because he seems to think that there was a difference in weight of the pregnant ewes.

Another point raised by Evans is the potential of clovers and their endogenous phytoestrogens to contribute to the changes we observed in our study (Paul et al. 2005). In the pastures in which these studies were conducted (55°N), there were minimal amounts of clover, even after several years of treatment with sludge; therefore, any contribution of this source to our study is almost certainly minimal.

Finally, we point out again that there were no significant differences between the control animals and those reared on sewage sludge–fertilized pastures in terms of the frequency of multiple births, so it is not appropriate to consider Evans' speculation regarding contributions that the mineral nitrogen might have made to this occurrence.

In summary, although we accept that there may be differences between the two types of pasture that may have contributed in some way to the present studies—for which we have been unable to control—we believe that our study achieved its primary goal: We established that exposure of pregnant ewes to a complex cocktail of environmental chemicals (those present in treated sewage sludge) could selectively affect development of the testes of male fetuses. We have not identified which chemical or mixture of chemicals caused this change, and we emphasized in our article (Paul et al. 2005) that to do so is a complex and probably impossible task. The important point is to prove the principal that exposure to mixtures of environmental chemicals at "real world" levels has the potential to alter male reproductive development.

The author declares he has no competing financial interests.

Richard Sharpe
MRC Human Reproductive Sciences Unit
Centre for Reproductive Biology
University of Edinburgh
Edinburgh, United Kingdom
E-mail: r.sharpe@hrsu.mrc.ac.uk

Reference

Paul C, Rhind SM, Kyle CE, Scott H, McKinnell C, Sharpe RM. 2005. Cellular and hormonal disruption of fetal testis development in sheep reared on pasture treated with sewage sludge. Environ Health Perspect 113:1580–1587; doi:10.1289/ehp.8028 [Online 11 July 2005].

Prenatal Phthalate Exposure and Anogenital Distance in Male Infants

In our article "Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure" (Swan et al. 2005), we reported results of our recent study on the relationship between anogenital distance (AGD) in boys and their mother's urinary concentration of phthalate metabolites (Swan et al. 2005).

The primary question we addressed was the relationship between the concentration of phthalate metabolites in maternal prenatal urine and the AGD, or the more appropriate derived measure anogenital index (AGI = AGD/weight), in human male offspring. We designed our study to focus on this specific measurement because of highly reliable results in the animal literature showing that certain phthalates reduce AGD (and AGI) in rodents and because, as continuous variables, AGD and AGI would not require a large sample size to demonstrate this relationship, if it existed. Changes in the frequency of a dichotomous and relatively rare end point such as frank cryptorchidism, also caused in animals by prenatal phthalate exposure, require far larger sample sizes. Secondarily, we looked at AGI in relation to other genital measurements (penile volume, testicular descent, and scrotal size), examining these interrelationships in several ways.

In our article (Swan et al. 2005), we reported that urinary concentrations of four phthalate metabolites [mono-*n*-butyl phthalate (MBP), monobenzyl phthalate (MBzP), monoethyl phthalate (MEP), and monoisobutyl phthalate (MiBP)] were inversely and significantly related to AGI. We also examined three metabolites of diethylhexyl phthalate (DEHP). Although the associations between AGD and the secondary DEHP metabolites [mono-2-ethyl-5-oxohexyl phthalate (MEOHP) and mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP)] were suggestive, they were not statistically significant, and the metabolite MEHP appeared to be unrelated to AGI.

We examined the relationship between AGI and testicular descent in several ways, varying whether each of these variables was entered into the analysis untransformed (e.g., as they were recorded in the examination) or as dichotomous variables.

AGD was measured by the examiner using a Vernier calipers. Both AGD and AGI are continuous, and approximately normally distributed, variables. The degree of descent of each testicle was categorized as follows: 0 = normal, 1 = normal retractile, 2 = high scrotal, 3 = suprascrotal, 4 = inguinal, and 5 = nonpalpable or ectopic. The testicular placement score (TPS) is the sum of the recorded value for the left and right testicle. Therefore, the lower the TPS, the more complete the testicular descent. We first examined the relationship between AGI and testicular descent by calculating the correlation coefficient between AGI and TPS (an ordinal variable). In the complete data set, including 134 boys with genital examination, AGI is significantly and inversely related to TPS (correlation coefficient –0.201, p-value 0.021). That is, shorter AGI was significantly associated with less complete testicular descent.

This analysis assumes that TPS is an interval variable; for example, the difference

between a score of 0 (both testicles "normal") and 1 (one testicle "normal" and one "normal retractile") is equal to that between 1 and 2 (either both "normal retractile," or one "normal" and one "high scrotal"). We also examined TPS as a dichotomous variable, which does not require this assumption. For this purpose, testicular descent was coded as 0 and called "complete" if both testicles were rated as either normal or normal retractile; otherwise, it was coded as 1 and called "incomplete." This dichotomous variable was also significantly correlated with AGI (correlation coefficient –0.192, *p*-value 0.027). Since results by these two methods were similar, we did not include this latter analysis in our article (Swan et al. 2005).

As is common practice in epidemiologic analyses, we also dichotomized AGI to create two groups to serve as cases and controls. For this purpose, we classified boys into "short" AGI (< 25% of expected for age) or "not short." We looked at the proportion of boys with incomplete testicular descent in these groups. We incorrectly stated the *p*-value for not short (0.136) in our article (Swan et al. 2005) to be statistically significant. That this analysis was not statistically significant, while the analysis of the AGI as continuous variable was, is not surprising; dichotomizing a continuous variable results in a loss of power, and thus a larger sample size is needed to achieve a similar level of statistical significance (Ragland 2002).

In conclusion, in all analyses boys with shorter AGI had less complete testicular descent, and significantly so for the two analyses in which AGI was treated as a continuous variable. The miscalculation of statistical significance for one analysis, while unfortunate, in no way alters any of our conclusions. Also, this error does not weaken this article's (Swan et al. 2005) support for the importance of examining patterns of subtle changes in humans, as suggested by toxicology, when assessing the effects of environmental exposures.

The author declares she has no competing financial interests.

Shanna H. Swan
Department of Obstetrics and Gynecology
University of Rochester
School of Medicine and Dentistry
Rochester, New York
E-mail: shanna_swan@urmc.rochester.edu

References

Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, et al. 2005. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect 113:1056–1061.

Ragland DR. 1992. Dichotomizing continuous outcome variables: dependence of the magnitude of association and statistical power on the cutpoint. Epidemiology 5:434–440.

Phthalates Not in Plastic Food Packaging

I am writing with regard to a misleading photograph and caption in the article "Children's Centers Study Kids and Chemicals" (Phillips 2005) published in the October 2005 issue of *EHP*. The article includes the following caption (p. A 665):

> **Mothers, babies, and chemicals.** Researchers are studying whether variations in the enzymes that metabolize the phthalates found in some plastic bottles correlate with later birth and growth outcomes.

Above the caption is a photograph of a mother-to-be holding a plastic water bottle. Contrary to both the photograph and caption, phthalates are not used in plastic beverage bottles, nor are they used in plastic food wrap, food containers, or any other type of plastic food packaging sold in the United States.

The term "phthalates," short for "orthophthalates," refers to a class of additives that are used in some plastic products, specifically products made with a particular type of plastic—polyvinyl chloride (PVC or vinyl)—to make the material soft and flexible. Vinyl shower curtains, cable, wire, and flooring are examples of flexible PVC products that can contain phthalates.

Plastic beverage bottles sold in the United States are made from a type of plastic known as polyethylene terephthalate (PET). Although polyethylene terephthalate (the plastic) and phthalate (the additive) may have similar names, the substances are chemically dissimilar. PET is not considered an orthophthalate, nor does PET require the use of phthalates or other softening additives.

Another article in the same issue, "Are EDCs Blurring Issues of Gender?" (Hood 2005), echoes this misperception concerning phthalates and plastic food packaging. The article, which discusses phthalates, contains a photograph of plastic beverage bottles (p. A675) and, in the last two paragraphs (p. A677), makes reference to both plastic wrap and Saran Wrap. As a point of clarification, phthalates are not used in plastic food wraps sold in the United States categorically, and SC Johnson's website specifically states that "… phthalates are not used in any Saran or Ziploc product" (SC Johnson 2006). The article (Hood (2005) also discusses bisphenol A, a substance used to make the plastic in some reusable water bottles, but not the convenience-size beverage packaging shown in the photograph.

The American Plastics Council respectfully requests that *EHP* address the misinformation that appeared in these articles and which is available on the *EHP* website.

The author is employed by the American Chemistry Council/American Plastics Council.

Patricia A. Enneking
American Plastics Council
Arlington, Virginia
E-mail: patty_enneking@plastics.org

Reference

Hood E. 2005. Are EDCs blurring issues of gender? Environ Health Perspect 113:A670–A677.

Phillips ML. 2005. Children's centers study kids and chemicals. Environ Health Perspect 113:A664–A668.

SC Johnson. 2006. Bogus E-Mail Attacking Plastic Wraps Refuted. Available: http://www.scjohnson.com/family/fam_pre_pre_news.asp?art_id=64 [accessed 12 January 2006].

Editor's note: The following erratum was published in the January 2006 issue (Environ Health Perspect 114:A21):

In the October articles "Children's Centers Study Kids and Chemicals" [Environ Health Perspect 113:A664–A668 (2005)] and "Are EDCs Blurring Issues of Gender?" [Environ Health Perspect 113:A670–A677 (2005)], photographs and their captions erroneously imply that plastic drink bottles contain ortho-phthalates. Plastic drink bottles sold in the United States are made from polyethylene terephthalate and do not contain ortho-phthalates. Also, at the end of the EDCs article, references are made to plastic wrap and Saran Wrap. For clarification, neither plastic wrap nor Saran Wrap contains ortho-phthalates. EHP *regrets these errors.*

Errata

Azziz-Baumgartner et al. noticed two errors in "Case–Control Study of an Acute Aflatoxicosis Outbreak—Kenya?" [Environ Health Perspect 113:1779–1783]. The units in Figure 2 and Table 2 should be nanograms per milligram instead of micrograms per milligram. The errors were introduced when new figures and tables were generated during the final revision of the paper. The authors apologize for these errors.

In the article by Feist et al. [Environ Health Perspect 113:1675–1682], the units were incorrect in several figures and tables: "Lipid (μg/g)" should be "μg/g lipid" in Tables 1 and 2 and in the *y*-axes of Figures 2 and 3A–C. Also, on the *y*-axes in Figure 5A–D, "dL" should be "mL." *EHP* regrets these errors.

The photograph on page A29 of the January 2006 NIEHS News section should have been credited to Jennifer Gorenstein/UTMDACC COEP. The photographs on page A30 should have been credited to Tom Van Biersel/Louisiana Geological Survey (left) and Bryan Parras/UTMB (right). Additionally, Parras's photograph depicts residents of Pointe-aux-Chenes, not LaRose, and includes no COEP staff.

In the Beyond the Bench article in this same section, "COEPs Contribute to Hurricane Relief" [Environ Health Perspect 114:A30–A31 (2006)], Peter Thorne was incorrectly identified as director of the University of Iowa COEP; he is in fact director of the University of Iowa Environmental Health Sciences Research Center as well as head of the NIEHS Working Group on Mold, Microbial Agents, and Respiratory Diseases. It was the latter group that "collected air and surface samples from water-damaged homes in New Orleans" as our article stated. Finally, the aid teams that traveled throughout Louisiana included members from the UTMDACC COEP as well as the UTMB COEP.

EHP regrets the errors.

In the January Focus article "In Katrina's Wake" [Environ Health Perspect 114:A32–A39 (2005)], Hurricane Katrina was identified as a Category 4 storm, reflecting statements from the National Hurricane Center as of press time. The National Hurricane Center has since reported that Katrina was actually a Category 3 storm at the time of landfall.