Correspondence

Regional Differences Invalidate U.S. Sperm Trend Conclusions

Regarding the continuing debate in EHP over the question of whether or not human sperm densities have declined in the United States, I feel compelled to respond to the statement by Swan et al. (1) that regional variation would not be inconsistent with the average decline that we demonstrated in Europe and the United States.

In referring to regional variation in sperm densities, Swan et al. cite the work of Fisch et al. (2) as indicating that sperm counts have not declined in the United States. In this study, sperm counts were analyzed in Los Angeles, California; Roseville, Minnesota; and New York, New York. A study by MacLeod and Wang (3) indicates that sperm counts have remained constant in New York since 1938. In addition, two other published studies report that sperm counts have not declined in Wisconsin (4) or in Seattle, Washington (5). There is not a single study of healthy men from any fertility center or sperm bank that has reported a decline in sperm counts in the United States.

The regional variation in sperm counts, with a nearly twofold difference in average sperm counts between Los Angeles and New York, invalidates any study that attempts to demonstrate a twofold decline in sperm counts based on trends over time in reporting of sperm counts from different regions of the United States (6). Despite the assertion of Swan et al. (7) that the data are robust, there can be no valid demonstration of a twofold decline in sperm counts in the United States when normal sperm counts vary nearly as much between Los Angeles and New York.

John Heineze
John Adams Associates
Washington, D.C.

REFERENCES AND NOTES
1. Swan SH, Elkin E, Fenster L. Response: A reanalysis of sperm density data. Environ Health Perspect 106:A370–A371 (1998).
2. Fisch H, Goluboff ET, Olson JH, Feldshuh J, Broder SJ, Barad DH. Semen analyses in 1,263 men from the United States over a 25-year period: no decline in quality. Fertil Steril 65:1005–1014 (1996).
3. MacLeod J, Wang Y. Male fertility potential in terms of semen quality; a review of the past, a study of the present. Fertil Steril 31:103–116 (1979).
4. Wittmaack FM, Shapiro SS. Longitudinal study of semen quality in Wisconsin men over one decade. Wis Med J 91:477–479 (1992).
5. Paulsen CA, Berman NG, Wang C. Data from men in greater Seattle area reveals no downward trend in semen quality; further evidence that deterioration of semen quality is not geographically uniform. Fertil Steril 65:1015–1020 (1996).
6. Fisch H, Goluboff ET. Geographic variations in sperm counts: a potential cause of bias in studies of semen quality. Fertil Steril 65:1044–1046 (1996).
7. Swan SH, Elkin E, Fenster L. Response: sperm density declines. Environ Health Perspect 106:A420–A421 (1998).

Peggy Davis
Atlanta, Georgia

Chlorpyrifos (Dursban) and Dow Employees

Papers published in EHP concerning adverse effects of pesticide exposure have helped protect the public's health. These include the study by Guillette et al. (1) concerning learning impairment in young children exposed to pesticides; the birth defects–pesticides study by Garry et al. (2); brain tumors in pesticide-exposed children (3); and the study by Gurunathan et al. (4) demonstrating volatilization and condensation of Dursban onto indoor surfaces, thus potentiating exposure.

The article by Gibson et al. (5) in the June issue of EHP raises a number of troubling questions. The authors failed to cite the reasons for EPA restrictions on the use of (chlorpyrifos) Dursban (6,7) and the EPA report that reviewed thousands of adverse reports to the EPA and poison control centers (8).

Gibson et al. (5) allege that chlorpyrifos is not mutagenic. Of the 28 Dursban toxicity tests reported in the EPA database for 1996, 19 were negative for gene mutation, 3 were positive for DNA damage, 1 was positive for aneuploidy, and 2 were positive for micronucleus disruption (9). Genetic damage was seen in applications of pesticides (10).

Gibson et al. (5) claim that chlorpyrifos is not teratogenic and does not adversely affect reproduction. In November 1996, under Section 6(a)(2) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), DowElanco itself reported 12 adverse reproductive effects to the EPA as a part of its late adverse reaction reports. A year later, Dow reported a thirteenth human case and adverse reproductive outcome in a breeder dog (11). The material safety data sheet for Dursban TC (12) states,

Fetotoxicity and fetal development abnormalities were observed in a chronic ingestion study of pregnant mice, but the same dose produced severe maternal toxicity.

Chlorpyrifos, the pesticidal agent in Dursban, is both a chlorinated and organophosphate chemical, with toxicity characteristics of each class of chemicals. The product Dursban is a complex mixture, containing sulfoatep and trichloropyridinol (TCP) in addition to chlorpyrifos. TCP is used to manufacture chlorpyrifos, is found in the commercial product, is the metabolic breakdown product, and has been reported to be teratogenic at doses that are nontoxic to the mother (13,14).

Goldsmith et al. (15) reported birth defect cases in Israel. These pesticide exposures included Dursban, and were also reported directly to the U.S. EPA (16). Still Dow has been reluctant to accept the consent that exposure to a chlorinated organophosphate chemical designed to kill insects by interfering with neurological function could harm the developing human. Whitney et al. (17) reported specific cellular mechanisms for developmental neurotoxicity.

Gibson et al. (5) cited only four children with birth defects [see Sherman (18)]. There actually were eight children with birth defects who had been exposed in utero to Dursban (19). Discussing the findings, Gibson et al. (5) claimed lack of "consistency of symptoms among the children." Actually, the findings are not symptoms, but actual defects, and there is a strong pattern, calculated at odds of 104-5 the first four children (20). Tabulation of eight children demonstrates a consistent pattern (see Table 1). In keeping with standard scientific methodology, other causes of birth defects have been explored (see Table 2).

Gibson et al. (5) state that I said "the mother's exposures to chlorpyrifos happened too late in the child's development
to be toxicologically significant." My statement was in response to a question from a judge in regard to another child that was not involved in the case under consideration (21). Although I expressed concern about testifying to fact in a case without the records before me and without the family being represented by their attorney, I was required to answer the judge's hypothetical questions. I testified (19) that the child's defects are the same pattern as the other seven children.... [And he [the child] follows the same pattern of the boys in that all boys had undescended testes.

When I reviewed the actual records, the record is clear: when the family home was treated with Dursban, the unborn son was an 11.5-week-old fetus. The child died at 7 years of age. His abnormalities, consistent with the reported pattern, were confirmed on autopsy. Thus, my testimony was not accurately represented by Gibson et al. (5). (Although I was paid to examine six of the children and to review the medical records of one child who subsequently died, I was not compensated for reviewing the documents for two of the children.)

To say that any mother's exposures to chlorpyrifos "happened too late in the child's development to be toxicologically significant" (5) would be inaccurate. Throughout intrauterine life, the developing fetus undergoes rapid cell growth, programmed cell death (apoptosis), and cell rearrangement, which are all time- and space-dependent. Intervention with any of these processes results in abnormalities of subsequent growth and development. The specific disruption of intrauterine development depends upon both the inciting agent(s) and the state of development of the embryo, expressed subsequently as anatomic and/or functional defects. Thus, exposure later in fetal development or in infancy will result in defects that differ from those produced earlier in development. One child exposed to Dursban as an infant (22) became essentially quadriplegic (21). Wargo (23), the National Research Council (24), and the Food Quality Protection Act of 1996 agree on the special vulnerability of children to pesticide exposure.

Gibson et al. (5) further state that "Sherman's work does not adhere to general scientific standards used in medical and clinical practice." In the child's case cited by Gibson et al., I examined the child; interviewed the mother, father, and brother; visited the workplace where the mother's exposure occurred; visited the home of the child; spoke with the treating physician; read all of the child's and mother's medical records; and submitted over 10,000 pages of documents, which I rely on for my opinion. I have also published other teratology reports that link chemical exposure during pregnancy to birth defects (25).

Gibson et al. (5) cited the judge who ruled against the family of one of the Dursban-affected children as saying, My tentative view is that Dr. Sherman's case studies do nothing more scientifically than to suggest a causal relation.

### Table 1. Birth defects in children exposed in utero to Dursban

| Defect                        | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    |
|-------------------------------|------|------|------|------|------|------|------|------|
| Sex of child                  |      |      |      |      |      |      |      |      |
| Brain defects                 |      |      |      |      |      |      |      |      |
| Structural deformities        |      |      |      |      |      |      |      |      |
| Ventricular                   |      |      |      |      |      |      |      |      |
| Microcephaly                  |      |      |      |      |      |      |      |      |
| Hydrocephaly                  |      |      |      |      |      |      |      |      |
| Atrophy of brain              |      |      |      |      |      |      |      |      |
| Abnormality type              | CC   | CC   | SP   |      |      |      |      |      |
| Eye defects                   |      |      |      |      |      |      |      |      |
| Structural                   | Mi   | Mi,C | Mi   | Cl   |      |      |      |      |
| Blind                         |      |      |      |      |      |      |      |      |
| Catarract                     |      |      |      |      |      |      |      |      |
| Palate abnormality            |      |      |      |      |      |      |      |      |
| Cleft lip                     |      |      |      |      |      |      |      |      |
| Tooth abnormality             |      |      |      |      |      |      |      |      |
| Nose abnormality              |      |      |      |      |      |      |      |      |
| External ear                  |      |      |      |      |      |      |      |      |
| Other                         | 7N   | AS   | AS   |      |      |      |      |      |
| Heart                         |      |      |      |      |      |      |      |      |
| Abnormal external             |      |      |      |      |      |      |      |      |
| Specific abnormality          |      |      |      |      |      |      |      |      |
| Genital                       |      |      |      |      |      |      |      |      |
| Abnormal external             |      |      |      |      |      |      |      |      |
| Other                         |      |      |      |      |      |      |      |      |
| Mental retardation            |      |      |      |      |      |      |      |      |
| Nipples wide-spread           |      |      |      |      |      |      |      |      |
| Foot abnormalities            |      |      |      |      |      |      |      |      |
| Hypotonia                     |      |      |      |      |      |      |      |      |
| Growth retardation            |      |      |      |      |      |      |      |      |

**Table 2. Review of medical history and chemical exposures**

| Findings                      | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    |
|-------------------------------|------|------|------|------|------|------|------|------|
| Chromosome studies            | N    | N    | N    | N    | N    | N    | N    | N    |
| Maternal smoking              | No   | No   | No   | No   | No   | No   | No   | No   |
| Maternal alcohol use          | No   | No   | No   | A    | No   | No   | No   | No   |
| Infections during pregnancy   | No   | PU   | No   | No   | No   | No   | No   | No   |
| Pregnancy medication use      | T    | S    | T    | O    | Ty   | Ty   | Pr   | 0    |
| Family history of birth defects|      |      |      |      |      |      |      |      |
| Child's mother                | 0    | 0    | 0    | 0    | 0    | 0    | 0    | CB   |
| Child's father                | 0    | 0    | 0    | 0    | 0    | 0    | 0    | LD   |
| Mat grandmother               | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Mat grandfather               | U    | U    | 0    | 0    | 0    | 0    | 0    | 0    |
| Pat grandmother               | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| Birth defects in other siblings |      |      |      |      |      |      |      |      |
| Other chemical exposures      |      |      |      |      |      |      |      |      |
| during pregnancy              | C    | 0    | 0    | F    | 0    | 0    | Cy   | D/B  |
| Dursban product used           | LO   | TC   | LO   | LO   | PU   | PU   | 270  | Sp   |

**Correspondence**

Environmental Health Perspectives • Volume 107, Number 3, March 1999
That there is a causal relationship, based upon human case finding, animal testing, biochemistry, and structure–activity relationships, is precisely the point. This has also been demonstrated by additional independent physicians and scientists and appears in various publications and court records.

The cost of caring for one of these totally dependent children is in excess of $500,000. The financial, emotional, social, and physical burdens upon the families is staggering. Prevention is imperative.

Janette D. Sherman
Alexandria, Virginia

1. Guillenette EA, Meza MM, Aquilar MG, Soto AO, Garcia JE. An anthropological approach to the evaluation of preschool children exposed to pesticides in Mexico. Environ Health Perspect 106:347–353 (1998).
2. Garry VF, Schreinemachers D, Harkins ME, Griffin J. Pesticide appliers, infants, and birth defects in rural Minnesota. Environ Health Perspect 104:394–399 (1996).
3. Pogoda JM, Preston-Martín S. Household pesticides and risk of pediatric brain tumors. Environ Health Perspect 105:1214–1220 (1997).
4. Gurunathan S, Robson M, Freeman N, Buckley B, Roy A, Meyer R, Bukowski J, Lioy PJ. Accumulation of chlorpyrifos on residential surfaces and toys accessible to children. Environ Health Perspect 106:9–16 (1998).
5. Gibson JE, Peterson RKD, Shurdt BA. Human exposure and risk from indoor use of chlorpyrifos. Environ Health Perspect 106:303–306 (1998).
6. Letter from LR Goldman, Assistant Administrator, Office of Prevention, Pesticides and Toxic Substances, U.S. EPA, to J Hagaman, President and CEO, DowElanco, 14 January 1997.
7. Sherman JD. Reply to JPD Maurissen’s letter to the editor. Toxicol Ind Health 13(1):91–93,95–97 (1997).
8. U.S. EPA memorandum from J Blondell and VA Boboy, Health Effects Division, to L Probst, Special Review and Reregistration. Review of chlorpyrifos poisoning data, 14 January 1997.
9. Jackson MA, Stark H, HF, Waters MD. Genetic Activity Profiles of Agents from the Long Island Breast Cancer Project. Research Triangle Park, NC:U.S. Environmental Protection Agency, 1996.
10. Garry VF, Tarbox RE, Long L, Griffin J, Kelly JT, Burroughs B. Pesticide appliers with mixed pesticide exposure: G-banded analysis and possible relationship to non-Hodgkin’s lymphoma. Cancer Epidemiol Biomarkers Prev 5:11–16 (1996).
11. Reports are available from U.S. EPA Office of Pesticides Programs, Washington, DC, under a Freedom of Information (FOI) request. Cases are reported under a numbering system named “DERBI” (DowElanco Research Business Index). These include the following DERBI numbers: 9920, 23154, 23178, 23194, 23296; 23397, 23436, 23575, 23577; 28735, and 23415.
12. Dow Chemical Co. Material Safety Data Sheet. Dow Dursban TC. Midland, MI:Dow Chemical Co., 1997.
13. Dow Chemical Co. Material Safety Data Sheet. Trichloropyridinol. Midland, MI:Dow Chemical Co., 1991.
14. Hanley TR Jr, Zieke DJ, Lomax LG. 3,5,6-Trichloro-2-pyridinol: Oral Teratological Study in New Zealand White Rabbits. Midland, MI:Dow Chemical Co., 1987.
15. Goldsmith JR, Kordysh E, Sobel R, Avnon L, Oryan I. Birth defects associated with agricultural chemicals used in some cooperative agricultural settlements. Presented at the International Symposium on Environment, Lifestyle and Fertility, 12–13 December 1997, Aarhus, Denmark.

16. Letter from JR Goldsmith to S Sullivan, U.S. EPA Office of Pesticides, 16 April 1997.
17. Whitney KD, Seidler FJ, Strock TA. Developmental neurotoxicity of chlorpyrifos: cellular mechanisms. Toxicol Appl Pharmacol 154:53–62 (1995).
18. Sherman JD. Chlorpyrifos (Dursban)-associated birth defects: report of four cases. Arch Environ Health 51(1):5–8 (1996).
19. National Bank of Commerce et al. (Edorado, AR) v. Dow Chemical Co., et al., Case No LR-C-94-64. U.S. District Court for the Eastern District of Arkansas, Little Rock, AR (testimony of JD Sherman), 12 September 1996.
20. Sherman JD. Chlorpyrifos (Dursban)-associated birth defects: a proposed syndrome, report of four cases, and discussion of the toxicology. Int J Occup Med Toxicol 4(4):417–431 (1995).
21. Sherman JD. Organophosphate pesticides—neurological and respiratory toxicity. Toxicol Ind Health 11(1):33–39 (1995).
22. J Herb, V Herb, SF Herb v. Dow Chemical Co. et al. Civil Action No 90-C-2420, Circuit Court of Kanawha County, WV, Charleston, WV, 1990.
23. Wargo J. Our Children’s Toxic Legacy. New Haven, CT:Yale University Press, 1996.
24. National Research Council. Pesticides in the Diets of Infants and Children. Washington, DC:National Academy Press, 1993.
25. Sherman JD. Chemical Exposure and Disease: Diagnostic and Investigative Techniques. Princeton, NJ:Princeton Scientific Publishing, 1994.

Response to Sherman

We find it unnecessary to address all statements made by Janette Sherman in her letter about our article in the June issue of EHP (1). It is important to note that the Centers for Disease Control and Prevention (CDC), the U.S. EPA, and the California EPA have each reviewed Sherman’s arguments and purported evidence and concluded that Sherman has failed to establish a legitimate association between human exposure to chlorpyrifos and teratogenicity. In a letter to Jerome Blondell of the U.S. EPA (2), the CDC commented on Sherman’s evidence as follows:

At the present, there does not appear to be a consistent phenotypic pattern of anomalies among the infants whose records we reviewed. In addition, you reported that [chlorpyrifos] is used extensively in the United States. Based on the available medical records and the likely high frequency of this exposure, we would be hesitant to recommend pursuing major epidemiological studies at this point in time.

Subsequently, on 14 January 1997, Blondell issued a memorandum (3) which stated that:

HED [the Health Effects Division of the EPA] concludes that available evidence does not support a finding of teratogenicity based on human epidemiology studies and case reports.

Similarly, in a memorandum dated 27 January 1997 (4), R. Cochran, staff toxicologist, of the Medical Toxicology Branch of the Department of Pesticide Regulation of the California EPA stated:

There was no scientific evidence presented in either paper by Dr. Sherman which supported the contention that chlorpyrifos could cause birth defects—either in laboratory animals or humans.

In addition to government scientists and regulators, two independent panels of scientific experts have comprehensively reviewed published chlorpyrifos toxicity and epidemiology studies, including Sherman’s papers, and both have rejected the scientific validity of any claims associating chlorpyrifos exposure with birth defects (5,6).

We stand behind our paper in all respects, and we feel that any objective review of the relevant data will strongly support our conclusions.

James E. Gibson
Dow AgroSciences LLC
Indianapolis, Indiana

1. Gibson JE, Peterson RKD, Shurdt BA. Human exposure and risk from indoor use of chlorpyrifos. Environ Health Perspect 106:303–306 (1996).
2. Letter to Jerome Blondell, U.S. Environmental Protection Agency, from JD Erickson, CA Moore, and HE Roberts, Centers for Disease Control and Prevention, 18 December 1996.
3. Memorandum from J Blondell and VA Boboy, Health Effects Division, U.S. Environmental Protection Agency, to L Probst, Special Review and Reregistration. Review of chlorpyrifos poisoning data, 14 January 1997.
4. Memorandum from R Cochran, staff toxicologist, Health Assessment Section, Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency, to G Peterson, supervising toxicologist, Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency. Review of DowElanco Study No JEG122396: Critical review of allegations associating Dursban with human teratogenicity, 27 January 1997.
5. Cleg DJ, van Gemert MA. Determination of the reference dose for chlorpyrifos: proceedings of an expert panel. J Toxicol Environ Health (in press).
6. Albers JW, Cole P, Greenberg RS, Mandel JS, Monson RR, Ross JH, Snogren WR, Spurgeon A, van Gemert M. Analysis of chlorpyrifos exposure and human health: expert panel report. J Toxicol Environ Health (in press).