

CORRESPONDENCE

Is vinclozolin a reproductive hazard to men?

Zober *et al*¹ examined fertility, hormones, and offspring sex ratio of men exposed to the fungicide vinclozolin. These authors were inclined to dismiss the possibility that it has any deleterious effect on the male reproductive system. I should like to suggest in contrast, that its effects in two respects resemble those of the nematocide dibromochloropropane (DBCP), which lowers sperm count² and is associated with a highly significantly lowered offspring sex ratio.³

Zober *et al*¹ report that although the testosterone concentrations of exposed men were unchanged their follicle stimulating hormone (FSH) concentrations were significantly higher than those of controls ($P = 0.004$). Similarly, increased FSH and unchanged testosterone were found in men exposed to DBCP.⁴ Increased gonadotrophin, or lowered testosterone concentrations, or both are characteristic of many illnesses in men.⁵

The offspring of men exposed to vinclozolin numbered 44 sons and 51 daughters.¹ Compared with an expected⁶ Caucasian live birth sex ratio (proportion male) of 0.515, these figures yield a χ^2 of 1.05 ($P < 0.15$, one way). So although not formally significant, they may be thought to be suggestive.

I suggest that further study of the possible effects of vinclozolin on the male reproductive system are merited. Its known similarities to an established hazard, DBCP, are disturbing. Especially interesting (and easy to gather) would be the sex ratios of offspring of men exposed to vinclozolin.

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- 1 Zober A, Hoffmann G, Ott MG, Will W, Germann C, Van Ravenzwaay B. Study of the morbidity of personnel with potential exposure to vinclozolin. *Occup Environ Med* 1995;52:233-241.
- 2 Whorton D, Krauss RM, Marshall S, Milby TH. Infertility in male pesticide workers. *Lancet* 1977;ii:1259-61.
- 3 Potashnik G, Yanai-Inbar I. Dibromochloropropane (DBCP): an 8-year re-evaluation of testicular function and reproductive performance. *Fertil Steril* 1987;47:317-23.
- 4 Whorton D, Milby TH, Krauss RM, Stubbs HA. Testicular function in DBCP-exposed pesticide workers. *J Occup Med* 1979;21:161-6.
- 5 Semple CG. Hormonal changes in non-endocrine disease. *BMJ* 1986;293:1049-52.
- 6 James WH. The human sex ratio. Part I: a review of the literature. *Hum Biol* 1987;59:721-52.

Authors reply—In his letter, James raises questions about two specific health outcome measures reported in our paper, namely, serum follicle stimulatory hormone (FSH) and sex of children born to fathers in the study group, and suggests that our findings for vinclozolin are similar to those reported by others for dibromochloropropane (DBCP), a known reproductive toxin in men.

As was pointed out by James, the mean value of the serum FSH measurements was significantly higher in the exposed than in the control group ($P = 0.004$ both before and after exclusions based on known pre-exposure health conditions) and this would suggest a possible causal relation between exposure and outcome. However, for both luteinising hormone (LH) and FSH, non-significant but negative dose-response trends were found relative to current intensity as well as estimates of cumulative dose of vinclozolin exposure (see fig 4 of original paper for scatter plot of FSH *v* current intensity measure). Also, the man in the exposed group whose FSH level of 14.0 mU/ml was at the upper limit of normal had unilateral atrophy only later found to have been present since childhood. All other readings among exposed men were within the reference range. From toxicological studies on vinclozolin and studies on other agents that block the testosterone receptor such as flutamide, the pattern of gonadotrophins at effective dose rates typically consists of increased testosterone, greatly increased LH, and marginally increased FSH concentrations.^{1,2} In the absence of dose-response and any abnormal FSH findings within the restricted exposed group and the lack of similarity between observed gonadotrophin patterns and what would be expected for an antiandrogenic agent, it is difficult to conclude that our findings are indicative of an effect related to vinclozolin.

Because the medical histories reported in table 3 of our paper did not distinguish between births occurring before and after first exposure, we reviewed the medical and work history data of all study group participants to find the number and sex of children born nine or more months after the date of the first exposure. Within this restricted observation period, there were 31 births, 13 male and 18 female, reported by 21 members of the study group. The number of births per family unit ranged from one to three. There were eight families with more male than female children born after exposure, 11 families with more female than male children and two families with one male and one female child born after exposure. These more detailed data are consistent with the trend noted by James, but are also consistent with a chance distribution of children by sex. Again available toxicological data for vinclozolin indicate that at toxicologically effective doses, it is not the sex ratio of offspring that is affected, but rather development in males.¹

A further issue raised by James was the resemblance between the effects of vinclozolin and those of DBCP on the basis of our FSH and sex ratio findings. From a toxicological viewpoint, there are few similarities between the two substances. DBCP has been shown to affect testicular tissue through direct genotoxic effects.³ Vinclozolin is not genotoxic and does not affect Sertoli cells directly, but rather acts by blocking the testosterone receptors.^{1,2} This mechanism of action is quite different from that of DBCP and the anticipated pattern of

gonadotrophin findings and their implications would be expected to be different as well.

In conclusion, we do concur with the suggestion that further systematic observation of people likely to have contact with vinclozolin is prudent and would be of scientific merit. However, we do not agree with the analogy drawn between vinclozolin and DBCP, which is not, in our opinion, supported by existing toxicological and epidemiological data.

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- 1 van Ravenzwaay B. Discussion of prenatal and reproduction toxicity of Reg No 83 258 (vinclozolin). Data submission to US EPA. Washington: BASF Corporation MRID, 1991. (No 425813-02.)
- 2 JMPR. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. Food and agriculture organization of the United Nations. Geneva: WHO 1995:191-4.
- 3 Lag M, Soderlung EJ, Omichinski JG, Brunborg G, Holme JA, Dahl JE, *et al*. Effect of bromine and chlorine positioning in the induction of renal and testicular toxicity by halogenated propanes. *Chemical Research in Toxicology* 1991;4:528-34.

Modifiers of non-specific symptoms in occupational and environmental syndromes

Editor—In a thorough review Spurgeon *et al*¹ concluded that various occupational or environmental factors may lead to an increase of non-specific symptoms such as headache, tiredness, eye irritation, and backache, when they are (rightly or wrongly) perceived as health hazards. Dissatisfaction with specific aspects of work may stimulate the occurrence of a similar pattern of health complaints. The authors discussed the role of individual and social factors in the perception of health and the tendency to report symptoms. Most probably some people are more sensitive to the psychosocial factors mentioned than others.¹

Spurgeon *et al* did not pay attention to one point. If anxiety and dissatisfaction affect the perception of health, there might be a comparable effect on the perception of environmental factors. If so, negative or anxious feelings may also intensify the reporting of complaints about aspects of work in a non-specific way.

Many studies in the field of occupational epidemiology are (at least partly) based on self reported health or work related exposures. It is obvious that the tendencies mentioned may lead to biased results. Any particular problem that crops up in a work situation may generate anxiety or dissatisfaction, which in turn stimulates the tendency to report non-specific symptoms and complaints. Assuming that this tendency is stronger in some people than others, spurious associations between exposure and effect can be expected. This is an additional reason to explore how psychosocial factors may colour the reporting of complaints.¹ Two topics should therefore be added to the recommendations for further research as formulated by Spurgeon *et al*.

(1) Empirical evidence should be searched for our hypothesis that feelings of anxiety or dissatisfaction may lead to increased complaints about (probably non-specific) aspects of work. Research done on

the sick building syndrome suggests that this may apply to both psychosocial and organisational factors as well as physical characteristics of work.²

(2) A valid method should be developed for the assessment of the psychosocial factors which seem to affect the perception and reporting of symptoms and complaints, to evaluate their influence in a particular study, and—if possible—to correct for their effects.

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- 1 Spurgeon A, Gompertz D, Harrington JM. Modifiers of non-specific symptoms in occupational and environmental syndromes. *Occup Environ Med* 1996;53:361-6.
- 2 Crawford JO, Bolas SM. Sick building syndrome, work factors and occupational stress. *Scand J Work Environ Health* 1996;22:243-50.

Author's reply—We thank the correspondents for their comments on our paper, and fully agree. The point that psychosocial factors may also affect awareness, and thus reporting of possible hazards in the workplace is well taken and supported by the literature. It was our intention that these aspects should be subsumed within the psychosocial pathway, particularly in relation to contextual factors, attitudes, beliefs, etc.

We also endorse the view that there is a need for a valid method to assess the influence of psychosocial factors on symptom reporting in relation to any particular hazard. This is particularly important in the workplace where the results of any such assessment should help to determine the focus of any prevention and control strategies. In many cases this focus may turn out to be psychosocial rather than, for example ergonomic, physical, or chemical.

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NOTICES

17th Annual New England epidemiology summer programme (5 and 10 day courses) June 9–July 4 1997. Tufts University, USA

The New England Epidemiology Institute summer programme at Tufts University's Medford campus includes methodological, statistical, and substantive courses. This programme is intended for those seeking an introduction to modern epidemiological concepts as well as those desiring a review of recent developments in epidemiological thinking.

Twenty five and 10 day courses cover the following: introduction to epidemiology, epidemiologic basis for causal inference, biostatistics for epidemiologists, clinical research, theory and practice of epidemiology,

epidemiology in developing countries, pharmacoepidemiology, meta-analysis, epidemiology in public health practice, clinical trials, survival analysis in epidemiology, decision and cost effectiveness analysis in health care, the biology and epidemiology of cancer, health care use and outcomes research, regression modeling in epidemiology, perinatal epidemiology, occupational and environmental epidemiology, molecular epidemiology and the use of biomarkers, ethics and epidemiology, and writing for publication in a scientific journal. Invited faculty include excellent teachers and prominent researchers from leading universities. Registrants may receive graduate-degree credit or continuing education credits from Tufts University, continuing medical education (AMA category 1) through Tufts University medical School, and certification maintenance from the American Industrial Hygiene Association.

Further information from: The New England Epidemiology Institute, Department PA-OEM, One Newton Executive Park, Newton Lower Falls, MA 02162-1450, USA. Phone: (617) 244-1200; Fax: (617) 244-9669; E-Mail: epidemiol@aol.com; World Wide Web Home Page: <http://www.epidemiology.com>

15th Asian conference on occupational health 31 August–3 September 1997. Kuala Lumpur, Malaysia

The theme of the conference is preparing for occupational health and safety needs of the next decade.

For more information on registration and presentation of papers, free communication, and posters at the conference please contact: Conference Secretariat, Society of Occupational & Environmental Medicine of MMA, 4th floor, MMA House, 124 Jalan Pahang, 53000 Kuala Lumpur, Malaysia. Tel: (60)(3) 4431740/4431743; Fax: (60)(3) 4418187.

9th International conference on occupational respiratory diseases. 13–16 October 1997. Kyoto International Conference Hall, Japan

The Conference is organised by the Japanese National Organising Committee for the Ninth International Conference on Occupational Respiratory Diseases, in collaboration with the Ministry of Labour of Japan, the International Labour Office and the Japan Industrial Safety and Health Association.

This Conference provides an excellent opportunity for scientists, health practitioners, hygienists, engineers, management, workers, and legislators to share experiences and ideas on the management and prevention of occupational respiratory diseases and to set priorities for the next century. The success of the meeting will depend upon contributions of papers and exhibits by leaders in the several disciplines of occupational health. We particularly encourage submissions from junior scientists, as well as from senior investigators.

Themes:

- Epidemiology of occupational respiratory diseases
- Health surveillance of workers exposed to

respiratory hazards

- Aetiology, pathogenesis, diagnosis and treatment of occupational respiratory diseases
 - Health hazard assessment by environmental and exposure monitoring
 - Control measures against health hazards at the workplace
 - Respiratory protective equipment
 - Information, education and training on occupational respiratory diseases
- Working Groups:
- ILO international classification of radiographs of pneumoconioses
 - Global action on elimination of silicosis
 - Occupational respiratory allergies
 - Natural and synthetic fibres
 - Relationship between occupational respiratory diseases and lung cancer

Further information from: International Communications Specialists, Kasho Building, 2-14-9 Nihombashi, Chuo-ku, Tokyo 103, Japan.

International symposium on environment, lifestyle, and fertility. 7–10 December 1997. Scandinavian Congress Center, Aarhus, Denmark

The symposium is organised within the framework of Asclepios (a European concerted action on occupational hazards to male reproductive capability).

Two European concerted actions have been launched with the objective of mapping the European occurrence of infertility and identifying occupational hazards to male reproductive function. Dozens of national studies in Europe, the United States, and throughout the world within reproductive epidemiology have provided additional knowledge to add to agreed recommendations for future research. There is a need to identify environmental risk factors as well as suspected factors with none or limited significance for infertility and there is a need to identify studies and methods to be recommended and not recommended.

The symposium will include the following state of the art reviews:

- The use of time to pregnancy in a demographic and epidemiological perspective: *Alfred Spira*
- Design and bias issues related to studies of subfertility: *Jørn Olsen*
- Validity of time to pregnancy data in men and women: *Michael Joffe*
- Semen quality as marker of fecundity in epidemiological studies: *Jens Peter Bonde*
- Endocrine markers of male fecundity: *Richard Sharpe*
- Impact of life style and social factors: *Nel Roeleveld*
- Occupational and environmental impact on fertility: *Steve Schrader*

The symposium is open for free communications related to the above topics and a poster session with plenary review will also be organised. The symposium language is English. Deadline for registration and submission of papers is 1 September 1997.

Further information from: Asclepios, Pia Pors/Jane Boilesen, Department of Occupational Medicine, The Steno Center of Public Health, Aarhus University Hospital, Noerrebrogade 37–39, DK-8000 Aarhus C, Denmark. Phone: +45 8949 4294; Fax: +45 8949 4260; E-mail: akh.gp22s.akamkpp1@aaa.dk