Letters to the Editor

Correspondence re: E. Hawk, *et al.*, Male Pattern Baldness and Clinical Prostate Cancer in the Epidemiologic Follow-Up of the First National Health and Nutrition Examination Survey. Cancer Epidemiol. Biomark. Prev., *9:* 523–527, 2000

Letter

Wendy Demark-Wahnefried[1] and Joellen M. Schildkraut

Program of Cancer Prevention, Detection and Control Research, Duke University Medical Center, Durham, North Carolina 27710

We read with great interest the recent paper by Hawk *et al.* (1), who reported that male pattern baldness was significantly associated with increased risk for prostate cancer. Given that the study relied upon a prospective design, a large sample, and data that were appropriately analyzed, the report makes a substantive contribution to the literature related to potential risk factors for prostatic carcinoma. However, there are some weaknesses in the study. First, as the authors acknowledge, male pattern baldness was defined as any sort of baldness that could be rated as "mild," "moderate," or "severe." Thus, specific data were not collected on the two major types of baldness patterns, *i.e.*, vertex and frontal. Given evidence from previous studies that both androgen levels and androgen receptor status may differ between men displaying these two distinct types of baldness patterns (2–4), as well as direct evidence that vertex baldness may be associated with increased risk of prostate cancer, whereas frontal baldness may not (5), we suggest that the odds ratios reported by Hawk *et al.* may be attenuated. Second, the reported odds ratios may be attenuated further given evidence that there may be an optimal period to assess baldness; *i.e.*, by age 30, if indeed it is used to portend risk (5). Finally, the age distribution of the men who were bald is also older than men who were not bald, which also may have lowered the magnitude of the reported odds ratios. In concluding this letter, we applaud the efforts of Hawk *et al.* and put forth the premise that the association that they found between baldness and prostate cancer may be even stronger, if indeed they had the ability to discriminate between vertex and frontal baldness and if baldness were assessed by age 30 in a higher proportion of their sample. Future studies that assess baldness at younger ages as well as ascertain data on specific baldness patterns are needed to determine whether or not baldness truly is a strong risk factor for prostate cancer.

References

1. Hawk, E., Breslow, R. A., and Graubard, B. I. Male pattern baldness and clinical prostate cancer in the Epidemiologic Follow-up of the First National Health and Nutrition Examination Study. Cancer Epidemiol. Biomark. Prev., *9:* 523–527, 2000.

2. Demark-Wahnefried, W., Lesko, S. M., Conaway, M. R., Clark, R. V., Lobaugh, B., Mathias, B. J., Strigo, T. S., Robertson, C. N., and Paulson, D. F. Serum androgens: associations with prostate cancer risk and hair patterning. J. Androl., *18:* 495–500, 1997.

3. Hibberts, N. A., Howell, A. E., and Randall, V. A. Balding hair follicle dermal papilla cells contain higher levels of androgen receptors than those from non-balding scalp. J. Endocrinol. *156:* 59–65, 1998.

4. Sawaya, M. E. Biochemical mechanisms regulating human hair growth. Skin Pharmacol., *7:* 5–7, 1994.

5. Demark-Wahnefried, W., Schildkraut, J. M., Thompson, D., Lesko, S. M., McIntyre, L., Schwingl, P., Paulson, D. F., Robertson, C. N., Anderson, E. E., and Walther, P. J. Vertex baldness and prostate cancer risk. Cancer Epidemiol. Biomark. Prev., *9:* 325–328, 2000.

Received 6/6/00; accepted 1/23/01.

[1] To whom requests for reprints should be addressed, at Box 2619, Duke University Medical Center, Medical Sciences Research Building 455B, Durham, NC 27710. Phone: (919) 681-3261; Fax: (919) 684-9990; Email: demar001@mc.duke.edu.

Reply

Ernest Hawk,[1] Barry I. Graubard, and Rosalind A. Breslow

NCI, Bethesda, Maryland 20892 [E. H., B. I. G.], and Centers for Disease Control and Prevention, Atlanta, GA 30341 [R. A. B.]

We thank Drs. Demark-Wahnefried and Schildkraut for their thoughtful comments about the merits and potential limitations of our study (1). We agree that our inability to specify the pattern (*i.e.*, frontal *versus* vertex) or rate of male pattern baldness may have attenuated our risk estimates for prostate cancer. As we discussed in the article, the source of data for our study, the Epidemiologic Follow-up Study of the first National Health and Nutrition Survey (NHANES I), did not include these characteristics. Whether our risk estimates were attenuated further by failing to assess baldness at some "optimal" point in time is an interesting question. Like Drs. Demark-Wahnefried and Schildkraut, we were interested in whether men with an earlier onset of baldness might be at greater risk for prostate cancer, but as we reported, we did not find this to be the case. To fully address this question however, additional follow-up of prostate cancer outcomes in the NHANES I cohort will be useful. Indeed, our study included data on the prostate cancer status (as of 1992) for 793 men <35 years of age at the time of entry into the cohort in the early 1970's. These men are just now reaching the age at which prostate cancer becomes most common. We agree that in addition to further follow-up of the NHANES I

[1] To whom requests for reprints should be addressed, at National Cancer Institute, Gastrointestinal and Other Cancers Research Group, Executive Plaza North, Suite 201, MSC-7322, 6130 Executive Boulevard, Bethesda, MD 20892.
Received 12/29/00; accepted 1/23/01.

cohort, other longitudinal studies with repeated, detailed assessments of baldness starting at younger ages that provide information on the specific patterns and rates of baldness throughout adult life would be helpful to determine whether baldness is, in fact, a strong risk factor for prostate cancer.

Reference

1. Hawk, E., Breslow, R. A., Graubard, B. I. Male pattern baldness and clinical prostate cancer in the Epidemiologic Follow-up of the First National Health and Nutrition Examination Survey. Cancer Epidemiol. Biomark. Prev., *9:* 523–527, 2000.

Correspondence re: Cummings *et al.*, Consumer Perception of Risk Associated with Filters Contaminated with Glass Fibers. Cancer Epidemiol. Biomark. Prev., *9:* 977–979, 2000

Letter

James E. Swauger

Scientific and Regulatory Affairs, R. J. Reynolds Tobacco Company, Winston-Salem, North Carolina 27105

A recent Short Communication by Cummings *et al.* raised a number of criticisms regarding Eclipse cigarettes (1). Because it is not possible in letter format to address all of the criticisms raised in the Cummings *et al.* article, this response is limited to the most significant issues raised in that article.

Eclipse is a new cigarette that produces smoke by primarily heating, rather than burning, tobacco. A glass mat insulator is an essential component of the heat source assembly used in Eclipse. The glass mat insulator is composed of continuous filament glass fiber and a binder.

Some scientists have expressed concern that continuous filament glass may be present on the outer surface of the Eclipse cigarette (2). RJRT[1] has previously responded to these concerns (3). Furthermore, RJRT has acknowledged that continuous filament glass may be present on the external surface of Eclipse cigarettes. However, the assertion that the utilization of continuous filament glass in Eclipse represents a potential toxicological concern to smokers is based on assumption and/or speculation rather than fact. To date, no evidence exists that demonstrates smokers are exposed to continuous filament glass at a level that may be construed to be biologically meaningful.

The potential transfer of continuous filament glass to Eclipse mainstream smoke has been studied. Subsequent to handling procedures that were designed to simulate commercial shipping conditions, cigarettes were machine-smoked using an exaggerated puffing regimen (relative to the United States Federal Trade Commission puffing regimen). These conditions were used specifically to maximize the probability that any potential transfer of continuous filament glass to Eclipse mainstream smoke would be detected. The results of studies conducted at RJRT indicate that a maximum of 0.143 filaments per cigarette are transferred to Eclipse mainstream smoke (4, 5). For perspective, survey data demonstrates that consumers are potentially exposed to literally thousands of glass filaments daily as a result of nonoccupational environmental exposure (6). It should be intuitive that any Eclipse-related exposure would represent a small fraction of potential background exposure. In short, the results of the transfer studies consistently indicate that, relative to background, biologically significant transfer of continuous filament glass to Eclipse mainstream smoke does not occur.

The assertion by Cummings *et al.* that the continuous filament glass used in Eclipse is respirable is inaccurate. The continuous filament glass used in Eclipse was designed to be nonrespirable. The continuous filament glass mat insulator is made from continuous glass filaments having an average diameter of 8.5 μm (range, 5.5–14 μm). These filaments are chopped to a length of 9500 μm and subsequently converted into a mat. The calculated aerodynamic diameters, parallel and perpendicular, of these filaments would be $\sim$53 μm (range, 35–84.4 μm) and 40.2 μm (range, 26.7–64.2 μm), respectively (7). It is generally accepted that structures with aerodynamic diameters greater than 7 μm (8, 9) are unlikely to reach the pulmonary region of the respiratory tract.

In a practical sense, if exposure does not occur, there can be no risk. The significance of this specific issue has not been lost on competent organizations that have addressed the potential toxicological activity of fibrous materials. The position taken by the National Toxicology Program (NTP) of the United States Department of Health and Human Services clearly indicates that the physical characteristics and, therefore, the respirability of glass filaments are relevant. In 1994, the NTP specifically listed glass wool (respirable size) as a substance "that may reasonably be anticipated to be a carcinogen" in the Seventh Annual Report on Carcinogens. It is noteworthy that the potential carcinogenicity of glass filaments (nonrespirable) in humans was not addressed.

The assertion by Cummings *et al.* that fibrous glass materials are as potent or more potent than asbestos is also inaccurate. Chronic inhalation studies have been conducted with rat respirable fractions of representative glass fibers (10, 11). In these studies, rats were exposed by nose-only to a rat-respirable (size-selected) fraction of two representative glass fibers (MMVF 10 and MMVF 11). Although crocidolite asbestos (the positive control) was demonstrably carcinogenic to rat lung, no statistically significant increase in fibrosis or lung tumors was observed subsequent to exposure to either MMVF 10 or MMVF 11 (10, 11). It is noteworthy that the intent of the study was, in fact, to deliver large numbers of "rat-respirable" fibers to the lungs of the rats studied.

In summary, transfer data and the unique physical characteristics of the filaments demonstrate that significant exposure of the smoker will not occur. The available environmental

Received 12/28/00; accepted 2/9/01.

[1] The abbreviation used is: RJRT, R. J. Reynolds Tobacco Company.

survey data clearly demonstrate that Eclipse smokers are extremely unlikely to be exposed to continuous filament glass at a level representing an increase relative to background exposure levels. Furthermore, the chemical composition and dissolution characteristics of the filament used in Eclipse demonstrate similarity to glass fiber compositions that have failed to produce either tumors or fibrosis in chronic inhalation studies conducted in rats. In short, exposure of Eclipse smokers to continuous filament glass is extremely unlikely to occur at a level that may be construed to be of biological significance. A formal safety assessment addressing this topic has been published in the peer-reviewed literature (12).

RJRT remains committed to providing accurate information to interested members of the scientific community. I would encourage interested parties to contact me directly for any further clarification required.

References

1. Cummings, K. M., Hastrup, J. L., Swedrock, T., Hyland, A., Perla, J., and Pauly, J. L. Consumer perception of risk associated with filters contaminated with glass fibers. Cancer Epidemiol. Biomark. Prev., *9:* 977–979, 2000.

2. Pauly, J. L., Lee, H. J., Hurley, E. L., Cummings, K. M., and Streck, R. J. Glass fiber contamination of cigarette filters: an additional risk to the smoker? Cancer Epidemiol., Biomark. Prev., *7:* 967–979, 1998.

3. Swauger, J. E. Correspondence re: J. L. Pauly *et al.*, Glass fiber contamination of cigarette filters: an additional risk to the smoker? Cancer Epidemiol. Biomark. Prev., *7:* 967–979, 1998. Cancer Epidemiol. Biomark. Prev., 8:835–838, 1999.

4. Higuchi, M. A., Ayres, P. H., Swauger, J. E., Morgan, W. T., and Mosberg, A. T. Analysis of potential transfer of continuous glass filament from Eclipse cigarettes. Inhal. Toxicol., *12:* 101–124, 2000.

5. Higuchi, M. A., Ayres, P. H., Swauger, J. E., Morgan, W. T., and Mosberg, A. T. Quantitative analysis of potential transfer of continuous glass filament from Eclipse prototype 9-014 cigarettes. Inhal. Toxicol., *12:* 1055–1070, 2000.

6. World Health Organization. Man-made mineral fibers and radon. IARC Monogr. Eval. Carcinog. Risks Hum., *43:* 33–87, 1988.

7. Baron, P. A. Measurement of asbestos and other fibres. *In:* K. Willeke and P. A. Baron (eds.), Aerosol Measurement: Principles, Techniques, and Applications, pp. 540–590. New York: Van Nostrand Reinhold, 1993.

8. Phalen, R. F. Inhalation Studies: Foundations and Techniques. Boca Raton, FL: CRC Press, 1984.

9. McClellan, R. O., and Henderson, R. F. Concepts in Inhalation Toxicology, pp. 85–171. New York: Hemisphere, 1989.

10. Hesterberg, T. W., Miller, W. C., McConnell, E. E., Chevalier, J., Hadley, J. G., Bernstein, D. M., Thevanaz, P., and Anderson, R. Chronic inhalation toxicity of size-separated glass fibers in Fischer 344 rats. Fundam. Appl. Toxicol. *20:* 464–476, 1993.

11. Rossiter, C. E., and Chase, J. R. Statistical analysis of results of carcinogenicity studies of synthetic vitreous fibres at research and consulting company, Geneva. Ann. Occup. Hyg. *39:* 759–769, 1995.

12. Swauger, J. E., and Foy, J. W-D. Safety assessment of continuous glass filaments used in Eclipse. Inhal. Toxicol. *12:* 1071–1084, 2000.

Reply

K. Michael Cummings,[1] Janice L. Hastrup, Richard J. Streck, Andrew Hyland, and John L. Pauly

Roswell Park Cancer Institute (K. M. C., A. H. A., R. J. S., J. L. P.) and State University of New York at Buffalo (J. L. H.), Buffalo, New York 14263

We are pleased that the R. J. Reynolds Tobacco Company (RJR) has finally acknowledged the validity of our 1998 publication documenting that the filters of Eclipse are contaminated with glass fibers and glass particles (1). However, Dr. Swauger's letter (2) regarding our recent paper (3) on consumer perception of risk associated with glass-contaminated filters illustrates that RJR does not consider the health concerns of consumers about the glass contamination of the Eclipse to be relevant.

Dr. Swauger cites recent studies (4, 5) conducted by RJR scientists who attempted to quantify the transfer of glass fibers into mainstream smoke. In these investigations: (*a*) five different prototypes, each identified by a code number only, were used; none of the prototypes were described, and they are not current market prototypes of Eclipse sold today; (*b*) in diverse assays, significant differences for the five prototypes were observed; yet no explanations were presented for the variability recorded; (*c*) a laboratory standard using earlier Eclipse prototypes was selected, and the studies did not include a proof-of-principle model that test-marketed Eclipse from partially filled packs that had been transported by smokers for several days; (*d*) values for glass fibers and glass particles on the filters of the various prototypes before and after smoking was not provided; and (*e*) the multistep and complex assay procedure used for assessing glass fiber transfer was associated with many shortcomings, some of which were acknowledged by the investigators (5). Inexplicably, RJR scientists have not replicated our original study protocol, which involved testing packs of Eclipse purchased from retail outlets as consumers would do. Moreover, our ability to respond to RJR's published studies on the transfer of glass to mainstream smoke has been blocked by the company's refusal to supply us with samples of the prototypes used in their studies.[2] In denying this request, RJR has declared that: "We have only some of the prototypes available and they are considered proprietary in nature".[2] For any company or investigator to invoke claims of unique materials in peer-reviewed publications and to not make the materials available to others for a confirmatory study is a breach of scientific conduct. This contemptuous behavior is disdainful to members of academic communities, scientific organizations, regulatory bodies, and others. Some journals (6) enforce this policy with a required submission form that must be signed by authors submitting manuscripts, in which they pledge that, "Unique materials described in this manuscript will be made available to qualified investigators."

We find RJR's assertion that there is no health risk from exposure to glass from Eclipse because the carcinogenicity of glass filaments in humans is still the subject of scientific debate to be imprudent. In science, there is an old saying that the "absence of evidence is not evidence of absence." Dr. Swauger's bias in reviewing the literature of glass fiber harm is illustrated by his failure to cite any epidemiological studies, animal experiments, or *ex vivo* research that have associated glass fibers with lung cancer and non-neoplastic pulmonary diseases or studies that have documented the presence of glass fibers in the lungs of rats (7) and human beings (8). We also do not believe that it is appropriate to make judgements about health risks based upon studies evaluating exposure to glass fibers in the environment when the actual exposure in question involves the use of a product that is intentionally and repeatedly placed directly into the consumer's mouth while inhaling deeply. RJR's safety claim for Eclipse also ignores the likeli-

Received 2/1/01; revised; accepted 2/9/01.

[1] To whom requests for reprints should be addressed at, Department of Cancer Prevention, Epidemiology & Biostatistics, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263. Phone: (716) 845-8456 Fax: (716) 845-8487; E-mail: Michael.Cummings@Roswellpark.org.

[2] J. L. Pauly and Mark Higuchi, personal communication.

hood that many users of Eclipse will already have damaged airways from years of smoking conventional cigarettes, thereby rendering them more susceptible to any potential health risks associated with exposure to glass fibers and particles.

Finally, Dr. Swauger ignores the main point made in our paper, which is that consumers perceive filters contaminated with glass to be a health concern (3). Whether or not RJR accepts the view that the inhalation of glass fibers poses a health risk is irrelevant to their obligation as the product manufacturer to inform consumers about their likely exposure to glass from smoking Eclipse and the unknown or potential risks that might result from such exposure.

In summary, RJR has advertised "reduced risk" health claims for a cigarette-appearing nicotine delivery device termed Eclipse that is available currently from retail stores and the Internet. RJR's claims are based upon studies of prototypes that RJR has refused to release to independent laboratories for objective analysis. RJR's reduced risk health claims of Eclipse promoted to smokers who cannot or will not quit smoking, many of whom seek a less harmful cigarette, has become a prime example illustrating the necessity to have an independent regulatory authority for tobacco products that will put the interests of the consumer before that of the manufacturer.

References

1. Pauly, J. L., Lee, H. J., Hurley, E. L., Cummings, K. M., Lesses, J. D., and Streck, R. J. Glass fiber contamination of cigarette filters: an additional health risk to the smoker? Cancer Epidemiol. Biomark. Prev., *7:* 967–979, 1998.

2. Swauger, J. E. Letter to the editor commenting on the paper by Cummings, K. M., Hastrup, J. L. Swedrock, T., Hyland, A., Perla, J., and Pauly, J. L. "Consumer perception of risk associated with filters contaminated with glass fibers. Cancer Epidemiol. Biomark. Prev. *9:* 977–979, 2000)." Cancer Epidemiol. Biomark. Prev., *10:* 416–417, 2001.

3. Cummings, K. M., Hastrup, J. L., Swedrock, T., Hyland, A., Perla, J., and Pauly, J. L. Consumer perception of risk associated with filters contaminated with glass fibers. Cancer Epidemiol. Biomark. Prev., *9:* 977–979, 2000.

4. Higuchi, M. A., Ayres, P. H., Swauger, J. E., Morgan, W. T., and Mosberg, A. T. Analysis of potential transfer of continuous glass filament from Eclipse cigarettes. Inhal. Toxicol., *12:* 101–124, 2000.

5. Higuchi, M. A., Ayres, P. H., Swauger, J. E., Morgan, W. T., and Mosberg, A. T. Quantitative analysis of potential transfer of continuous glass filament from Eclipse prototype 9-014 cigarette. Inhal. Toxicol., *12:* 1055–1070, 2000.

6. Information for Authors, The Editorial Policies and Practices of The Journal of Immunology, and Submission Form. J. Immunol., *165:* 593–602, 2000.

7. Hesterberg, T. W., Miiller, W. C., McConnell, E. E., Chevalier, J., Hadley, J. G., Bernstein, D. M., Thevenaz, P., and Anderson, R. Chronic inhalation toxicity of size-separated glass fibers in Fisher 344 rats. Fund. Appl. Toxicol., *20:* 464–476, 1993.

8. Infante, P. F., Schuman, L. D., Dement, J. and Huff, J. Fibrous glass and cancer. Am. J. Indust. Med., *26:* 559–584, 1994.

Correspondence re: E. Hawk, *et al.*, Male Pattern Baldness and Clinical Prostate Cancer in the Epidemiologic Follow-Up of the First National Health and Nutrition Examination Survey. Cancer Epidemiol.Biomark. Prev., *9:* 523–527, 2000

Wendy Demark-Wahnefried and Joellen M. Schildkraut

Cancer Epidemiol Biomarkers Prev 2001;10:415-416.