

Comments on "Comparative Hazards of Chrysotile Asbestos and Its Substitutes: A European Perspective"

I was glad to read the abstract of Harrison et al. (1) on the Web; this paper supports our work currently being done. I just returned from a cooperative program in Australia with Forestry and Forest Products-CSIRO, where methods were being developed to replace asbestos in fiber-cement products.

In the study in Australia, a new approach is being taken by using only alternative raw materials such as ground iron blast-furnace slag (BFS) as a matrix and cellulose fibers from sisal and banana crop wastes or eucalyptus pulp by-products.

The fibers were pulped using chemical and/or thermomechanical processes. The composites were prepared by a slurry vacuum de-watering method. The initial test results showed that physical and mechanical performance is acceptable for housing requirements. Long-term aging is now in progress in Melbourne, Australia, and Sao Paulo, Brazil, to evaluate durability. Further CSIRO/USP collaborative studies are planned to study BFS-based composites optimization and low-cost construction components related to walling and roofing.

Additional information is available from CSIRO (www.ffp.csiro.au/publicat/onwood/onwood22).

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Comments on "A Critical Review of Epidemiologic Studies of Radiofrequency Exposure and Human Cancers"

Elwood (1) made some important omissions in his critical review of radiofrequency radiation (RFR) and cancer.

Elwood referred extensively to the report by myself and others (2) on childhood leukemia in proximity to television (TV) towers in Sydney, Australia. He noted that the relative risk (RR) for childhood leukemia incidence was 1.58 [95% confidence interval (CI), 1.1-2.3] and more so for mortality 2.3 (CI, 1.4-4.0). He then

referred to the studies of Dolk et al. (3,4) of cancer near TV/ultrahigh frequency (UHF) transmitters in the United Kingdom as negative studies with regard to our study. In our letter (5), in which we commented on Dolks' UK studies, we pointed out that Dolks' studies did not examine for mortality. Elwood (1) did not discuss our novel finding of greater risk for mortality than incidence, which is suggestive of adverse survival, or that this observation has not been negated by other studies.

Elwood (1) also discussed a paper by McKenzie et al. (6), which was a reanalysis of our original data. Neither McKenzie et al. (6) nor Elwood (1) mentioned that the original hypothesis was that the group of three municipalities that immediately surround the TV towers would differ from the next six municipalities surrounding the towers (ring) with regard to leukemia. We treated the municipalities in each ring as a group, and we reported tests of homogeneity ($p = 0.10$ for incidence and $p = 0.13$ for mortality) between the inner municipalities in the original paper, which is shown in detail in our rebuttal letter (7). That there were some differences between the three municipalities is to be expected. However, it violates the original hypothesis to disaggregate the three inner municipalities, thus ignoring their homogeneity, to retrospectively conduct individual comparisons.

Elwood (1) contrasted the U.S. Naval Study by Robinette et al. (8), which apart from lung cancer found no excess cancer, with the Polish Military Study by Szmigelski (9), which found an excess of cancer at several sites including esophagus and bowel, as well as lymphohematopoietic and brain cells. Elwood (1) suggested that a systematic bias arose in the Polish study when data were collected on RFR exposure on cancer cases. However, all jobs had been previously measured and classified as exposed or nonexposed to RFR. All new cancer cases were individually reassessed regarding exposures. It is not obvious where the bias arose.

Elwood (1) noted that a weakness in the U.S. Naval study (8) is that it compared groups with high and low ($>$ or $<$ 1.0 mW/cm²) exposures and lacked an unexposed group to assess if the low-exposure group was truly unaffected. This is more than a weakness because both high and low exposure groups took recreation on decks where they were exposed to RFR, occasionally up to 1 mW/cm² according to Robinette et al. (8). This is important given Szmigelski's finding of effects occurring at $<$ 0.1 mW/cm², and may explain the null findings of the U.S. Naval study. Also, Szmigelski (9) stated that exposures

were 150-3,500 MHz, whereas the U.S. Naval study simply stated that microwave radar was $>$ 300 MHz. The importance of this difference is that the lower frequencies (150-300 MHz) in the Polish study (9) include wavelengths that have much greater coupling with the body, which in turn may contribute to a different spectrum of cancer sites.

Early in his paper, Elwood (1) noted that there is evidence that RFR may be a promoter of cancer. However, he did not consider the implications of this when discussing the study of brain tumors by Thomas et al. (10). Thomas et al. (10) found an increased risk of brain tumors (RR 2.3) in individuals who had both been exposed to RFR and worked in electronics, which would have likely caused exposure to solvents and fumes. A promotional effect of RFR is consistent with this observation.

Finally, in "Acknowledgments" Elwood mentioned that his paper was "stimulated by a request from Telecom New Zealand for a review of this topic." He did not mention that 2 months before submission of the paper, he had appeared as the major witness for Telecom NZ in a court case regarding placement of a mobile phone tower beside a primary school (11). I was called by the school to give evidence about the Sydney study.

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Radiofrequency Exposure and Human Cancers: Elwood's Response

I thank Hocking for his interest in my review (1). In regard to his own study (2), I put more emphasis on the incidence than the mortality results for several reasons. The interpretation of the mortality results is more complex, requiring control for confounding by prognostic factors (such as stage at diagnosis and precise age) as well as by risk factors for incidence. The difference between the relative risks for incidence and for mortality is not statistically significant, and of course the two results are not independent. The incidence results are also more useful because they can be compared with those of another study. The discussion in the paper by Hocking et al. (2) is almost all on the incidence relationship. The suggestion that radiofrequency radiation (RFR) exposure is related to adverse survival is a new hypothesis generated from these results and, as far as I know, has not been assessed in other studies.

The comparison of the two studies of childhood leukemia in Sydney, Australia (2–4), involves a comparison of concepts. In his letter, Hocking claims that the original hypothesis for these studies was that the leukemia rate in the three areas close to the TV towers would be different from the rate in the six areas farther away; as stated in my review (1), his statistical analysis depends on this comparison. However, in my opinion, the original hypothesis is epidemiological—whether there is an increased cancer incidence (and mortality) in children exposed to RFR from TV towers; this is given as the objective in the first paper by Hocking et al. (2). The use of a statistical design that compares two sets of areas is one way to assess this. This approach is not unreasonable but ignores the information provided by the comparison of each individual area. Such data are relevant to the assessment of the consistency of any association, which is an important aspect in assessing causality. I was surprised that the results by individual municipality, which Hocking et al. had available, were not given in the original paper (4), as I believe they affect the interpretation. The subsequent analysis showed that the excess was seen in only one of the

three areas close to the TV towers (3). Because of statistical variability, this does not rule out the general association seen by Hocking et al., but it shows inconsistency and weakens the argument that the association seen is caused by RFR from the TV towers rather than from any other cause.

In the Polish military study (5), the published report states that information on possible carcinogenic factors and RFR exposure was available for cancer cases from hospital records, in addition to data from other sources available for all personnel. This raises the possibility of systematic bias, as some information on exposure is available only for affected subjects. This potential bias has been noted independently in another detailed epidemiologic review (6). In regard to the U.S. Navy study (7), Hocking emphasizes the major weakness of the study, which I have noted. I agree that this study is very limited in exposure information.

In the case-control study of brain cancers, Thomas et al. (8) found a significant excess risk in electronics workers with no exposure to RFR, and no excess risk in those exposed to RFR who were not electronics workers. There was an increased risk in electronics workers who were also exposed to RFR, but this risk was lower than the risks for all electronics workers. Although this may be consistent with some complex promotional effect, the more parsimonious explanation is that the increased risk in electronics workers is due to some exposure other than RFR.

In his letter, Hocking refers to a New Zealand environment court case (9) that concerned a proposed Telecom cell phone transmitter site near a school. I appeared as an expert witness for Telecom, and he appeared as a witness for the school. My published review (1) was developed at the same time as my written evidence, but was not submitted until after the case in order to benefit from legal review as well as from scientific peer review. The legal hearing has resulted in a detailed judgment in favor of Telecom (9). In his judgment, Judge Jackson commented on each of the several expert witness submissions. He noted that “Elwood's evidence was carefully constructed and balanced” (9).

In summary, although the points raised by Hocking are worthy of note, I do not agree that any of them represent “important omissions” in my review paper.

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Comments on “What Is a Tumor Promoter?”

In the August issue of *Environmental Health Perspectives*, Raymond Tennant (1), shared his

perspective on how the identification of tumor promotion relates to the assessment of human health risk from environmental carcinogens.

I would like to reply to several of his statements. Although a complete reanalysis of his perspective is beyond this letter, I recommend additional reading (2–6). My comments are based on looking at the multistep, multimechanism process of carcinogenesis from a completely different paradigm, based on different assumptions.

Tennant (1) states that

The role of the tumor-promoting agents has not been so specifically defined, even in the most well-studied mouse skin model.

It has been known for over 20 years that a testable hypothesis exists, based on a specific cellular mechanism; this hypothesis is supported by data derived from molecular oncological, biochemical, cellular, and now knockout mouse data (2,7). This mechanistic model, namely, the reversible inhibition of gap junctional intercellular communication (GJIC), is as complete, if not more so, than our detailed mechanistic understanding of “initiation,” which is assumed to be related to DNA damage and mutagenesis.

Tennant (1) stated that "... few, if any, DNA reactive or genotoxic substances are only tumor initiators." Here, an assumption is being made that the DNA reactive or genotoxic substance [determined in an imperfect assay, such as the Ames test, sister chromatid exchange, thymidine kinase minus, hypoxanthine-guanine phosphoribosyltransferase, comet, micronucleus, and unscheduled DNA synthesis assays (8-11)] is, in fact, genotoxic. Even if an agent can damage DNA and lead to a mutation, the agent can cause cell death at significant exposures. Cell death can then lead to compensatory hyperplasia of the surviving cells. In addition, not all cytotoxic agents or hyperplastic-inducing conditions (burned tissue, surgery, etc.) damage DNA or cause mutations. There is an argument that these hyperplastic conditions cause mutations indirectly by causing surviving cells with nonlethal DNA lesions to have mutations fixed by DNA replication. Although in principle this is possible, it does not explain the fact that animals can be exposed to DNA-damaging agents, but promoted months later, after the DNA has been repaired. In addition, Tennant ignored the fact that spontaneously initiated cells exist in all organisms. Therefore, an agent that kills cells or acts as a mitogen, but is not a mutagen, could promote a previously existing spontaneously initiated cell. This could provide an alternative explanation to Tennant's statement that long-term repetitive treatment with either DNA reactive or nonreactive substances can result in the initiation/promotion and progression of tumors. The fact that "for the vast majority of substances that are carcinogenic, repetitive exposures are required," supports my contention that most of the so-called carcinogens (tested at high doses and for long periods of time) are, in fact, not true mutagens. Most are nongenotoxic, epigenetic substances. These substances are false positives in insensitive genotoxic assays or because the artifacts are ignored in these assays; this leads to the substances being misidentified as mutagens (8-11).

Tennant's (1) third assumption is that initiation or induction of mutations occurs in "appropriate target cells." Although I agree that carcinogenesis is the result of a small population of target cells being susceptible to neoplastic transformation (the pluripotent stem cells) (7,12), this has implications related to the necessity of some chemicals to be metabolized into electrophiles in order to damage DNA and induce mutations. When a rat is fed a chemical and a biochemist/molecular biologist grinds up a liver, extracts DNA, and searches for DNA lesions, he/she will find them. However, the hepatocytes (those cells with the drug-metabolizing

enzymes) make up the greater portion of the DNA being analyzed. Only a few of the cells in the liver are the target or stem cells. Therefore, extrapolating from the exquisite molecular analyses of DNA lesions from nontarget cells to the tumor in the animal fed a chemical does not prove the chemical caused the mutation in an oncogene/tumor-suppressor gene found in the rat tumor.

Tennant did not mention the hypothesis of GJIC inhibition of tumor promotion. This hypothesis is based on the operational observation of the action of promoters *in vivo*; namely, promoters must be given after the initiation (hours, days, weeks, months, or in the case of humans, presumably years), consistently exceeding no-effect or threshold levels for extended periods. The early steps of promotion are reversible or interruptible. This cannot be explained by any mutagenic or irreversible process ascribed to initiators. Mutagenic events are, for practical purposes, irreversible. Promoters must lead to the clonal multiplication of the single initiated cell. This clonal expansion of initiated cells is the result of both a mitogenic process due to an increase in the birth of new cells and the prevention of the death of initiated cells [inhibition of apoptosis (13)]. Normal quiescent or G₀ cells are contact inhibited (14). Tumor promoters release cells from contact inhibition by involving the inhibition of GJIC (15).

I take issue with Tennant's statement (1) that

...there is no information such as chemical structure or *in vitro* effects to reliably predict potential non-DNA reactive carcinogens.

There are many papers [including studies of DDT, dieldrin, polybrominated biphenyls, polychlorinated biphenyls, dinitrofluorobenzene, pentachlorophenol, etc. (16-18)] that predicted the tumor-promoting activity *in vitro* using the GJIC assay before testing *in vivo*. Moreover, more recent papers have, in fact, shown structure-function relationships that correlate inhibition of GJIC and tumor promotion (19-21).

Finally, I have a few comments related to the use of genetically modified mice and the DNA microarray technology. The connexin 32 knockout mouse may be the best model to search for tumor initiators of the rat liver because the mouse is a constitutive promoter (22) and because it has lost one of its tumor-suppressing genes. The use of DNA microarray technology to identify genes associated with non-DNA reactive carcinogens may be likened to closing the barn door after the horses have escaped. Some tumor-promoting chemicals can inhibit GJIC very early (minutes), induce signal transduction, posttranslationally modify proteins (p53), alter gene expression, induce DNA synthesis, and lead

to cell proliferation in the few target cells. Studying gene expression profiles in normal tissues (with few stem cells, more progenitor cells, and many terminally differentiated cells, all in different stages of the cell cycle and all expressing different genes, and a few apoptotic cells) and comparing treated or diseased tissues (with each cell type in different stages of the cell cycle and with different reactions to a given chemical) will generate bewildering patterns of gene expression, most of which will not reflect what goes on in the few target cells.

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Tumor Promoters: Tennant's Response

Trosko indeed presents an alternative and valid position on the nature of tumor promotion. It is certainly true that disrupted

intracellular communication is an important component in the promotion and development of tumors and may be another pathway by which repetitive exposure to nongenotoxic carcinogens and genotoxic carcinogens results in altered heritable cell phenotypes. The editorial in *EHP* (1) was not meant to be an exhaustive catalog of all of the various mechanisms by which nongenotoxic carcinogenesis can occur. It is clear that intercellular and intracellular signaling via endocrine, exocrine, paracrine, and autocrine pathways is critical in maintaining phenotypic stability. Evidence also suggests that when gap junctional intracellular communication pathways are disrupted, the frequent consequence is altered gene expression. Preliminary experiments (2) do not suggest that exposure of skin to nongenotoxic carcinogens or to a tumor promoter results in a bewildering pattern of changes in gene expression. We believe that it is plausible that analysis of time-dependent changes in the pattern of gene expression will provide an understanding of cell-signaling pathways that are altered by chemical exposure. It may also result in the recognition of biomarkers of critical events in the neoplastic process that will include disrupted gap junctional communication.

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CORRECTION AND CLARIFICATION

In the November *EHP*net article “Connecting for Kids” [*EHP* 107:A553], we wrote of the Children’s Environmental Health Network (CEHN): “Currently, this public interest organization is lobbying the U.S. Environmental Protection Agency (EPA) to require testing of pesticides for their effects on the developing nervous systems of children.” Although the CEHN is an advocacy group, it does not lobby specific pieces of legislation. *EHP* regrets any confusion this wording may have caused.