CORRESPONDENCE

Ingestion of herring leads to absorption of pristane in humans

Editor—Pristane (2,6,10,14-tetramethylpentadecane) is a branched chain hydrocarbon which is thought to be derived from the phytol moiety of chlorophyll. This compound has been associated with several biological effects. Pristane can induce plasmacytomas,¹ and together with some polycyclic aromatic hydrocarbons, act as promoters in the development of B-lymphoid malignancies and skin tumours in animals.^{2,3} Intraperitoneal injections have induced arthritis in mice.⁴

Pristane occurs in rather high concentrations, 1% to 3% of the body fat, in certain zooplankton and these plankton are assumed to be the primary source of the pristane found in liver oils of sharks and whales.⁵ Pristane is also found in herring and the concentration in flesh is about 370 µg/g of wet weight.⁶ Other fish species such as cod have much lower concentrations of pristane in their flesh, most often < 1 µg/g of wet weight.⁶

One of us (BS) volunteered to ingest Atlantic herring as lunch at 11 00 am. Four different meals contained 125, 140, 250, and 310 g of cured herring. A reference meal was composed of chicken with potatoes, hard bread, and water.

The quantitative analysis of pristane was performed with gas chromatography equipped with a flame ionisation detector. Pristane was also identified with gas chromatography-mass spectrometry, operated in electron impact mode. The recovery of the complete clean up method was >90% for pristane and the internal standard (dodecylcyclohexane). The detection limit of the method was 300 pg.

The serum concentration of pristane increased to 20–3000 ng/g serum 2–4 hours after ingestion of herring. Pristane was not detected before and 24 hours after ingestion of herring and it was not detected after the reference meal.

This experiment showed that pristane is clearly absorbed after the ingestion of Atlantic herring.

Pristane injected intraperitoneally into mice induces seropositive arthritis in susceptible strains. This agent has been proposed as an experimental model for rheumatoid arthritis.⁴ Swedish fishermen eat more herring than the general population⁷ and it is an interesting finding that fishermen had a high prevalence of rheumatoid arthritis when this disease was investigated in 66 large occupational groups in Sweden.⁸

It is also interesting that pristane is absorbed after ingestion of herring and this absorption should be studied in larger groups of humans after ingestion of herring and other species of fat fish. Further work is also needed to scrutinise the possible link between pristane exposure and the occurrence of multiple myeloma and diseases affecting the joints.

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Digestive tract neoplasms among employees with past exposure to brominated dioxins

Previously, we reported biomonitoring, immunological, and other clinical findings for a group of 42 employees potentially exposed to polybrominated dibenzo-p-dioxins (PBDDs) and furans (PBDFs) during extrusion blending of resins containing polybrominated diphenyl ether (PBDE) flame retardants.^{1,2}

In the five years since the clinical study was completed, two cases of digestive tract neoplasms have come to our attention within this group of employees and an additional digestive neoplasm was reported in a technician who performed analyses in support of the production operation including testing by pyrolytic methods. The two cases in the earlier study group had the highest observed 2,3,7,8-tetrabromodibenzo-p-dioxin (2,3,7,8-TBDD) concentrations in blood lipids among the 42 persons surveyed.

Case 1 was diagnosed to have squamous cell carcinoma of the oesophagus in January 1994 at the age of 57 and died nine months later. This person worked as an extruder operator throughout the period when PBDEs were used in the extruding operations (1977–89). He had the highest recorded 2,3,7,8-TBDD concentration (527 parts per trillion (ppt) measured in 1989) of any person in the study population. Other dioxin and furan congeners were increased as well with a 2,3,7,8-TBDF concentration of 176 ppt and total hepta- plus octa-TBDD concentrations of 10 000 ppt. Other factors potentially relevant to his diagnosis included

a history of smoking about one pack of cigarettes a day for 40 years and consumption of two to three bottles of beer a day.

Case 2 was diagnosed to have adenocarcinoma of the duodenum, a relatively rare type of cancer, in April 1994 at the age of 49 and died in July 1994. He had performed laboratory support work since 1974. Potential contact with PBDDs and PBDFs would have occurred between 1977 and 1989. Postmortem measurement of dioxins and furans in blood lipids showed a non-detectable 2,3,7,8-TBDD concentration, and a 2,3,7,8-TBDF concentration of 10 ppt. Marginally higher concentrations of the measured congeners were obtained in a fat sample as well as detectable concentrations of both 2,3,7,8-TBDD (0.8 ppt) and 1,2,3,7,8-penta-BDD (2.3 ppt).

Case 3 was diagnosed to have tubular adenoma of the rectum in September 1995 at the age of 48. He had also been employed as an extruder operator during the entire period of PBDE use. His initial 2,3,7,8-TBDD blood lipid concentration in 1989 was 425 ppt.

Case 1 is of particular interest because of our earlier findings of increased digestive and respiratory cancer among people with high chlorinated dioxin exposures who were also cigarette smokers.³ The remaining two cases represent contrasting occurrences where dioxin concentrations were less clearly higher than background (case 2) or where the tumour diagnosed was a relatively common benign neoplasm (case 3).

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Factors affecting recognition of cancer risks of nuclear workers

Editor—I have a problem with Kneale and Stewart's approach to statistical analysis and that is the fact that the more statistical tests they run on the same data, the more likelihood there is of encountering spurious or artefactual associations. For this reason the more nested tests, correction factors, and optimised values introduced into tests, the more likely the results will be significant but of no practical consequence. Surely the Hanford data have now been worked to death.

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Author's reply—Both the analyses of Hanford data which O'Donnell finds so unnecessary, and the 1991 analysis of Oak Ridge data by Wing *et al.*¹ have produced evidence of incompatibility between the records of nuclear workers recently released by the

United States Department of Energy (DOE data) and the records of A-bomb survivors that are the mainstay of radiation safety regulations in this country and elsewhere (A-bomb data). Also, analyses of the Hanford data have shown that for one variable of the relative risk model—that is, the one which measures the effect that the age when exposed has on the subsequent cancer risk, which should have a constant value whatever the source of the radiation—there is incompatibility not only between A-bomb data and DOE data but also between Hanford and Oak Ridge data and between Hanford data for different exposure periods.

What is evidently exasperating O'Donnell is not the number of times that Hanford data have been analysed (which is far fewer than the number of analyses on the A-bomb data) but the number of independent variables in the Kneale and Stewart relative risk model. Correct assessment of these variables is essential for future tests of important hypotheses, such as whether young people are more or less sensitive to cancer effects of radiation than old people, and whether A-bomb survivors apart from their radiation dose are or are not representative human beings. So it is clearly important not to stint on the time spent recognising false elements in DOE and A-bomb data.

Finally, we have a special reason for making this point, as we hope shortly to publish a paper which shows that the A-bomb survivors who most closely resembled the non-survivors—that is, the survivors who had multiple acute injuries, such as burns, purpura and epilation—differ in several important respects from the much larger number of survivors who had no such injuries.²

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1 Wing S, et al. Mortality among workers at Oak Ridge National Laboratory: evidence of radiation effects in follow-up through 1984. *JAMA* 1991;265:1397-401.

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Mesothelioma in a community in the north of England¹

Editor—Muir, who wrote a brief essay on the subject of bias in the field of occupational health in the final issue of the *British Journal of Industrial Medicine*,² will find this paper useful for teaching purposes. He might take issue with the authors on the literary style and presentation of historical facts, and on their analysis of data. We are informed that Acre Mill was commandeered in 1939 to produce gas mask filters. Reference to Defence of the Realm powers for initiating asbestos work might be misread by the reader as a plea in mitigation for the heavy harvest of asbestos disease resulting from post-war exposures. The introduction cites Bertram Mann as making some reference to problems resulting from asbestos exposure at the factory. Readers taking the trouble to rout out the text of his 1978 Royal College of Physicians Milroy lecture, will find that this chest physician had a lot to say about the amount of disease that he came across in this small part of his catchment area.

The discussion section states that: "In common with many asbestos factories, working conditions in respect of asbestos

dust were poor, especially in the early years of its operation." This might be misread to imply that conditions in its latter days were acceptable. Sir Alan Marre's (The Ombudsman) report in 1976 of his inquiry into Acre Mill, although concerned solely with the question of maladministration, did find that the factory was a cause for concern. The authors' statement that; "The factory closed in 1970 and has since been demolished," is incomplete. After Cape quit, it was occupied by another manufacturer for several more years, in a not entirely decontaminated state.

In the discussion section we are informed that between 2000 and 3000 people worked at the factory, although the material and methods section is not explicit on this point. One may assume that the authors did not have access to the nominal roll of employees. Otherwise they would surely have used the Registrar General's facilities for tracing and flagging the total population. No researcher should be faulted when making the best of limited data, provided the necessary caveats are presented prominently.

In their calculations, the authors gave an average incidence of tumour in Calderdale over the period 1966-94 as "12.5/million persons/year". This figure results from the dilution by the overwhelming non-exposed population. When the factory population is studied separately, the rate works out not surprisingly as between 524 and 786 cases of mesothelioma per million person-years depending on which extreme estimate of factory population is taken. For the non-exposed, the rate works out as 3.2 million person years, which is a higher rate than one would like to see in such a group.

The authors state that there were no neighbourhood cases of asbestos related disease. Yet of the 17 cases of malignant mesothelioma reported in the population not exposed to asbestos, eight had excessive amounts of amphibole in their lung tissues. We are not informed of how this might have been acquired. It is possible that despite the Pennine geography and meteorology exposure conditions were little healthier with respect to malignant mesothelioma than in the "dust bowls" of Barking and North Western Cape province.

Apropos quantitative fibre counts in the lungs (which commonly means the parenchyma, rarely the pleura, and even more rarely the bronchus), toxicologists look at the science of xenobiotic disease differently from pathologists, mineralogists, statisticians, and physicians. Physicians looking at disease in the pleura or peritoneum are content to relate it to the amount and type of fibre in the lung parenchyma rather than the type and quantity that has presented to the critical tissues. (Yet it is chrysotile rather than the amphiboles that is more often reported by pathologists to be found juxtapleurally.) Again, although physicians are content to discount the toxicity of chrysotile fibre because of its rate of clearance from the body, toxicology requires a better understanding of the toxicokinetics and mode of action of an agent. Animal experiments have not been conducted on the various asbestos species to relate their carcinogenic effects, dose for dose, fibre for fibre when equal dimensions are involved, but crude studies have indicated that they can share similar carcinogenic power. The courts are led to think that one can differentiate between the tumour caused by asbestos and the tumour not so caused, on an estimation of parenchymal

mal fibre content. This is despite the wide confidence limits that need to be placed around an estimate involving uncertainties in sampling and in counting, and despite the overlap in the distribution curves for lung fibre content between people with a history of asbestos exposure and those with no ascertainable exposure.

As for the authors' more sanguine attitude to chrysotile, the reader would be well advised to await the forthcoming review of chrysotile in the *Environmental Health Criteria* series published as part of the *International Programme on Chemical Safety*. This has had a stormy passage but is due out soon.

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Authors' reply—Greenberg's repeated concern that parts of our article might be misread is touching but likely to underestimate the perceptiveness of your readers. It is difficult to imagine how the factual statement that Acre Mill was "commandeered by the Home Office in 1939" could be construed as a "plea in mitigation for the heavy harvest of asbestos disease". Likewise his concern that our observations about working conditions might be misread to "imply that conditions in the latter days were acceptable". We wrote this article not with the purpose of apportioning blame but to set the medical scientific record straight about the number of cases of mesothelioma found in Calderdale. Even after rereading the article we do not recognise any suggestion that the working conditions at Acre Mill were any better or worse than any other asbestos factory working at that time. Perhaps David Muir might find this letter by Greenberg an interesting example of bias for teaching purposes.

Two of the authors (ATE and DW) worked alongside Bertram Mann for many years and his paper is well known to us. Despite his claims (in words or in writing) about asbestos related disease arising from asbestos pollution from the factory a detailed analysis of *tissue proven mesotheliomas* failed to detect any such case in a person living within two to four square miles of the factory who had not been employed at Acre Mill. Furthermore ATE performed most of the postmortem examinations in the district from 1960 to 1994 and has examined the reports of those not performed personally and he is not aware of any case of asbestos related disease occurring as a result of atmospheric pollution from the factory. This is despite a high level of awareness of asbestos related disease among the medical profession and in the community whereby suspected cases were readily referred to the local coroner.

We had very good access not only to senior ex-management of the mill but to many other ex-employees who are still alive and who had worked during wartime and later periods leading up to the time of closure. DW carried out personal interviews with many to gather information about the type of asbestos used and the working conditions. Several of DW's immediate family had worked at Acre Mill from the 1940s to