Formaldehyde exposure and leukaemia

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A new causal hypothesis?

"All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action it appears to demand at a given time." (Bradford Hill, 1965)

Scientific knowledge is never complete.¹ Scientists are sometimes surprised by new findings which question well established causal hypotheses. One hypothesis which has been accepted for several years and is now being questioned is that for formaldehyde carcinogenicity, particularly at low levels of exposure and in relation to cancer sites other than the upper respiratory tract.

Formaldehyde is currently classified by IARC as a probable human carcinogen based on animal studies with neoplastic lesions at the point of contact, the nasal cavity, but limited evidence of human respiratory tract carcinogenicity.² This IARC classification is based on several long term chronic bioassays, mechanistic information developed over 20 years, and 39 epidemiology studies. The studies on formaldehyde carcinogenicity represent one of the more extensive databases that IARC has reviewed.

Formaldehyde causes nasal cavity tumours in rats and at higher exposure levels in mice. The mechanistic information seems to indicate that formaldehyde at high airborne concentrations increases the occurrence of damage to the nasal cavity and this damage contributes to "the subsequent development of cancer".² However, there is thought to be no or little transport of formaldehyde beyond the point of contact since formaldehyde is rapidly metabolised and detoxified on contact with the upper respiratory tract. Thus, the focus of formaldehyde epidemiology for many years has been on cancers of

the upper respiratory tract as evinced by 25 case-control studies examining formaldehyde exposure and sinonasal cancer, nasopharyngeal cancer, lung cancer, and cancers of oral cavity, oropharynx, and hypopharynx, and 14 cohort studies examining exposure-response relations largely among the cancers of the respiratory tract. Rates of other cancers distant from the respiratory tract have been increased in some of the cohort studies; these findings have not received much attention.

The cohort studies of workers with formaldehyde exposures have been conducted in three broad occupational groups that have the potential to receive significant formaldehyde exposure—embalmers, anatomists, and industrial workers. The industrial worker studies have more direct and quantified estimates of formaldehyde exposure relative to the other groups.² While embalmers and anatomists have higher rates of brain cancer, lymphatic or haematopoietic cancers, and pancreatic cancers in some studies,³ the lack of higher rates of these cancers in the studies of industrial workers has been used to argue against a causal association.² The industrial worker studies in general have leukaemia rates close to expected levels.³

Two recent updates of large industrial studies, conducted in the United States by Hauptmann *et al* and Pinkerton *et al*, have found a positive association between selected measures of formaldehyde exposure and increased leukaemia rates,^{4,5} but a recent large industry-wide study of industrial workers with formaldehyde exposure by Coggon *et al* in the UK failed to confirm the finding.⁶ This study, which had more workers with higher exposures than both the Hauptmann *et al* and the Pinkerton *et al* studies combined, found no increase in risk of leukaemia in the highest exposure category. There are two areas where the findings leukaemia risk conflict with our current understanding of formaldehyde carcinogenicity, the lack of consistency of the data across epidemiology studies and biological plausibility.

For many putative occupational and environmental carcinogens, there is scant mechanistic information to help focus the research or contribute to causal assessment. However, this is not the case for formaldehyde as the mechanism for cancer in laboratory animals is well understood. The proposed association between formaldehyde and leukaemia does not appear consistent with the current biological evidence. In particular: (1) no evidence of toxicity at sites remote from the respiratory tract has been found, despite multiple long term inhalation animal bioassays; (2) no DNA-protein cross-links have been discovered in the bone marrow of rats exposed to high concentrations of formaldehyde; (3) formaldehyde does not occur in increased concentrations in blood when humans, monkeys, or rats are exposed to airborne formaldehyde; and (4) even very high concentrations of formaldehyde do not seem to cause cytogenetic damage in the lymphocytes and bone marrows of rats.²

New scientific findings in this well established field are useful because they force us to reconsider the evidence and determine what additional research may be needed to improve our understanding of the causal process. In the case of formaldehyde exposure and leukaemia, two research approaches seem possible. First, the two recent industrial studies which report a leukaemia effect should be critically reviewed to rule out uncontrolled confounding as far as possible and to assess the appropriateness of the comparison group that led to such unexpected findings. This approach could be pursued quickly, but would probably not bring the issue to resolution. Second, all of the available information should now be evaluated systematically to specify the additional research we need. Such additional research might include a formal evaluation of the leukaemia risk in previously published cohort epidemiological studies, updating some of the older investigations, formally analysing leukaemia rates by exposure level in all of the cohort studies, and investigating which mechanisms, if any, would allow formaldehyde to cause leukaemia. This approach, however, may take years to advance understanding. We are certain today that formaldehyde at high exposure levels increases nasal cancer in rats and mice. We are still debating whether or not humans exposed to far lower levels of formaldehyde are at any increased risk of cancer of the upper respiratory tract. As for the new leukaemia hypothesis, I suspect we are many years from resolution, but we do not have the "freedom to ignore the knowledge we already have, or to

postpone the action that it appears to demand".¹

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