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Letter to the Editor

LETTER TO THE EDITOR

Hematologic and cytogenetic biomarkers of leukemia risk from formaldehyde exposure

Enrico Pira, Canzio Romano, Carlo La Vecchia[1] and Paolo Boffetta[2,*]

Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy, [1]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy and [2]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

*To whom correspondence should be addressed. Tel: +1 212 824 7378; Fax: +1 212 849 2566; Email: paolo.boffetta@mssm.edu

Sir,

The causal nature of the association between formaldehyde exposure and risk of leukemia reported in some epidemiology studies (see (1) for review) has been questioned by the results of recent original studies and re-analyses, including some published by us (2–4).

A number of articles published in *Carcinogenesis* (5–7) and elsewhere (8–10), that reported the results of analyses of data derived from a cross-sectional study of hematologic and cytogenetic biomarkers (11), have been used to support a causal interpretation of the findings of some of the epidemiology studies. Although these articles pose and discuss interesting hypotheses, it is not clear that the data, as obtained and reported, validly support the conclusions of the authors (9,10,12).

The failure of the original study authors to adhere to the protocol of counting a minimum number of 150 cells in establishing the prevalence of cytogenetic abnormalities is a potentially important problem (9,13). In the Lan *et al.* study (5), the presentation of the data related to prevalence of monosomy 7 and trisomy 8 does not allow the reader to determine the number of cells that were counted, and the studies by Seow *et al.* (6) and Bassig *et al.* (7) relied upon the same results.

Another potential problem is that the original study and subsequent analyses were 'ecological': exposure and biomarker data were compared at the group (i.e. 'exposed' versus 'unexposed') level, precluding any valid representation that observed associations reflect any dose–response relationship or even change from a lower to higher level due to exposure (9,10). By referring to the cross-sectional prevalence of indicators in terms of 'changes', even the title of one of the original studies ('Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells' (11)) suggests a methodology that actually might document the movement of individual study outcome measures in response to an exposure event.

In addition, despite the overlapping data used across the three studies, some are described as confirmatory: 'Our current findings confirm our earlier findings that formaldehyde exposure was associated with aneuploidy in cultured circulating myeloid progenitor cells in vivo' (5). The current findings are, at least in part, the earlier findings, as the samples used for the aneuploidy analysis were likely from some of the same workers.

Furthermore, Gentry *et al.* (9). noted that although collected and described in Zhang *et al.* (11), individual formaldehyde exposure data were not used in these analyses. Mundt *et al.* obtained the formaldehyde exposure data for each exposed worker from this study, and performed extended analyses that demonstrated no exposure relationship for any of the haematological or cytogenetic markers, specifically monosomy 7 or trisomy 8 (10).

The analyses by Mundt *et al.* (10) of the original Zhang *et al.* (11) data were the first to present results by actual exposure data and draw into question some of the interpretations offered by the original authors (5–7,11). Lan *et al.* argued that an exposure-response analysis could not be conducted because of the narrow range of exposure (5). In fact, the 10th–90th percentile of the distribution of formaldehyde exposure concentration ranged between 0.8 and 2.5 ppm, a threefold range above the US Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) of 0.75 ppm (10).

We appreciate the efforts of many colleagues contributing to identify potential biological mechanisms by which exogenous formaldehyde exposure might be related to leukemia risk. However, the underlying data and statistical analyses appear not to meet basic methodological standards. Alternative explanations for associations seen between the combined groups of exposed and unexposed workers—but not across measured exposure concentrations—have never been explored. The questionable inferential value of the monosomy 7 and trisomy 8 prevalence findings based on methods deviating from protocol also needs to be addressed. Replication of these results in

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high-quality studies conducted in independent populations is needed before conclusions can be drawn on putative mechanisms of formaldehyde-induced leukaemia in exposed humans.

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