

Commentary

Updating IARC's Carcinogenicity Assessment of Benzene

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The task of updating more than 900 *IARC Monographs* evaluations developed over nearly four decades is immense. At times, IARC devotes a meeting to an updating of prior evaluations. Supplement 7 updated the assessments of all agents that had been reviewed in Volumes 1–42 [IARC, 1987]. Volume 71 updated the assessments of more than 120 of the agents that had been classified in IARC Groups 2A, 2B, and 3 (*probably carcinogenic to humans*, *possibly carcinogenic to humans*, and *not classifiable*, respectively) [IARC, 1999]. And for the most recent update to be published as Volume 100, IARC convened six meetings to update the assessments of the 107 agents now classified in Group 1 (*carcinogenic to humans*). Dr. Infante writes as an Observer¹ invited to the last of these six meetings, which was held in October 2009 and which focused on chemical agents and related occupations. All were reaffirmed as *carcinogenic to humans*.

IARC convened a special Advisory Group to get ideas about how best to develop the updates in Volume 100, then asked another Advisory Group to further review the preparations before convening the six meetings [IARC, 2007, 2008a]. As a result of their recommendations, IARC formed six separate Working Groups, each covering a related subset of the 107 agents. IARC also used the immediately preceding volumes to update several Group 1 chemical agents that had not been reviewed for many years: Volume 97 (June 2007) updated 1,3-butadiene, ethylene oxide, and vinyl

chloride; Volume 98 (October 2007) updated painting; and Volume 99 (February 2008) updated 4-aminobiphenyl, benzidine, dyes metabolized to benzidine, 4,4'-methylene-bis(2-chloroaniline), 2-naphthylamine, *ortho*-toluidine, auramine production, and magenta production. In addition, benzo[a]pyrene and six related occupations had been recently updated in Volume 92 (October 2005). Overall, 19 of the 33 agents considered in October 2009 had been updated very recently, thus there were relatively few new data to consider for these 19 agents and they took up a small fraction of the 8-day meeting. Most of the meeting was devoted to the remaining 14 agents. This is comparable to the number of agents updated at the other five Volume-100 meetings and also at the two previous meetings that considered benzene (Volume 29, 1982; Volume 7, 1974), where benzene was one of 18 or 23 agents, respectively, reviewed.

Dr. Infante raises several procedural issues, mostly centered on the limited time allowed for benzene. In fact, the most extensive discussions at the meeting were on benzene (and also on formaldehyde and dioxin). Moreover, the epidemiologists formed two subgroups to discuss the other 30 agents in parallel, so more time could be devoted to discussions of these three agents with all epidemiologists present from both subgroups. Dr. Infante also questions whether enough experts would be sufficiently familiar with the benzene literature to be able to make sound evaluations. In fact, there were several experts who had published original studies on the carcinogenicity of benzene. In addition to epidemiologists, there were several experts on mechanisms of leukemia induction. IARC has great confidence in the ability of Working Groups to reach sound evaluations. A Working Group comprising experts on benzene and experts on other carcinogens allows comparisons of the weight of evidence for different compounds. The experts found strong evidence of leukemia/lymphoma not only for benzene, but also for 1,3-butadiene, formaldehyde, rubber manufacturing,

¹Observers at *IARC Monographs* meetings come from constituencies with differing perspectives. In the interest of transparency, they are invited to observe the meeting and should not attempt to influence it [IARC, 2006].

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Accepted 13 September 2010

DOI 10.1002/ajim.20916. Published online in Wiley Online Library (wileyonlinelibrary.com).

dioxin, ethylene oxide, and painting [Baan et al., 2009]. Thus, the October 2009 meeting included frequent discussions of human leukemia and had a broad base of expertise to reach robust conclusions.

Dr. Infante makes much over 40 of 100 epidemiology studies being available electronically and the rest only on paper. In fact, 40 would reflect a count of benzene epidemiology studies initially available to the Working Group via an ftp site; this count grew to 300 studies, analyses, letters, and commentaries by the time of the benzene evaluation. Study data were extracted and arranged into extensive tables to facilitate the Working Group's simultaneous consideration of results for the same leukemia subtype from multiple studies. Many, if not most, of the cancer studies Dr. Infante claims were not included were, in fact, summarized in these tables. Most omissions are of two sorts: studies where benzene was one component of a complex exposure (e.g., in the rubber production industry) and unpublished reports that include more extensive results than the subsequent peer-reviewed journal articles. These cases will be discussed separately.

In the first case, Dr. Infante finds it contradictory that benzene has *limited evidence* for chronic lymphocytic leukemia while the rubber production industry (where benzene was used as a solvent) has *sufficient evidence* for leukemia (most of which was chronic lymphocytic leukemia). There is no contradiction, as *sufficient evidence* means chance, bias, and confounding could be ruled out with reasonable confidence and *limited evidence* means chance, bias, or confounding could not be ruled out [IARC, 2006]. The possibility of leukemia induction by other rubber-industry solvents can be a confounder for attributing leukemia in the rubber production industry to benzene specifically, while it is not a confounder for attributing leukemia to rubber production generally. Similar considerations apply to studies where benzene was one of many compounds in gasoline, in the petroleum industry, and in paints and paint solvents. The Working Group was mindful of the need to rule out confounding when making an evaluation of *sufficient evidence*, hence they decided give more weight to studies with estimates of benzene exposure rather than broader or surrogate measures such as solvent exposure generally or proximity to petrol stations. This would explain the absence of the childhood leukemia studies and many other studies Dr. Infante claims were missing (though, in fact, many were nonetheless summarized for discussion in the tables).

In the second case, it is useful to reiterate the *Monographs'* guidelines on studies that can be considered: the Working Group may consider reports that are publicly available and in final form [IARC, 2006]. This would apply to reports of the Australian Petroleum Industry Health Surveillance Programme, published on the Internet by the University of Adelaide. The Working Group was free to consider

this information if they felt the need to go beyond the peer-reviewed articles published in *Occupational and Environmental Medicine*. On the other hand, the Delzell et al. [1992] study, referenced by Dr. Infante only as "submitted to Union Oil Company," would not meet this criterion. These examples hint at a need for disclosure of risks found but not published in peer-reviewed journals. Dr. Infante alleges that the highest risks from the Australian Petroleum Industry Health Surveillance Programme were not published in *Occupational and Environmental Medicine*, and also that positive results for multiple myeloma and non-Hodgkin lymphoma were reported in Delzell et al. [1992] but not published in Sathiakumar et al. [1995]. The solution to this problem is not immediately apparent. Considering unpublished company reports carries its own risks of introducing unverified information into the evaluation process. But if Dr. Infante's allegations are correct, there is a larger problem of undisclosed risks that must be addressed by the cancer research community at large.

There is no disagreement with Dr. Infante's eight recommendations. The first, that a future meeting be focused on benzene, was already accepted at the October 2009 meeting, where some experts mentioned an ongoing quantitative meta-analysis that might clarify exposure-response relationships and contribute to causal inference for different subtypes of leukemia/lymphoma. Recommendations 2 and 3, that the epidemiology review include all settings involving benzene exposure, is already prerogative of any Working Group. We might note that the first two categories Dr. Infante mentions in Recommendation 3, paint and rubber solvents, are among the 33 agents reviewed in October 2009. Recommendations 4 and 5 to include industrial hygienists and pathologists is standard operating procedure, and these areas of expertise were present in October 2009. Recommendations 6 and 7 about discussion time and unpublished reports were examined above. Recommendation 8, that experts complete working papers so they can be reviewed before the meeting, is one that IARC wholeheartedly endorses.

Assessing the carcinogenicity of benzene is a complex undertaking. Many studies have investigated potential associations of benzene with different subtypes of leukemia and lymphoma, including childhood leukemia. Diagnosis and classification of leukemias and lymphomas have undergone fundamental changes over the past decade, incorporating genetic information and new molecular insights [WHO, 2001, 2008]. With this information and insight, lymphocytic leukemias and lymphomas are no longer considered to be different diseases [IARC, 2008b]. The Working Group was well aware of how this complicates the analysis of past cohort and case-control studies, which were conducted at different times and used different classification systems and were often based on the limited information available on death certificates.

The title page of each volume of *IARC Monographs* states, “This publication represents the views and expert opinions of an IARC Working Group . . .” and we are not going to use this space to second-guess the Working Group or to debate Dr. Infante’s expert opinion. Suffice it to say that there continues to be consensus that benzene is *carcinogenic to humans* and that it is a known cause of human leukemia. The previous benzene evaluation in Volume 29 found *sufficient evidence* for acute myelogenous leukemia and inadequate evidence for other malignancies [IARC, 1982]. The October 2009 Working Group strengthened this conclusion, and there is now *sufficient evidence* for acute non-lymphocytic leukemia and *limited evidence* for acute lymphocytic leukemia, chronic lymphocytic leukemia, multiple myeloma, and non-Hodgkin lymphoma [Baan et al., 2009]. There is a continuum between *sufficient evidence* and *limited evidence*, not a “bright line” that demarcates relationships that are causal from those that are not. Scientific judgment plays a role here, and individual scientists can legitimately reach varying conclusions about the evidence on each subtype of leukemia/lymphoma.

We thank Dr. Infante for his interest in and attention to the *IARC Monographs*. There is less disagreement here than there is agreement.

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