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Commentary

The IARC October 2009 Evaluation of Benzene Carcinogenicity Was Incomplete and Needs to Be Reconsidered

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I have been familiar with the toxicological and epidemiological literature on benzene since I was a member of the NIOSH Benzene Task Force in 1975. I also am familiar with the procedures of IARC Monographs meetings from past participation, and as observer I applied this experience to the Monograph 100 F review. In October of 2009, a Working Group (WG) of the International Agency for Research on Cancer (IARC) met in Lyon, France to evaluate the available evidence for site-specific cancer to humans for 33 chemical agents and related occupations previously categorized by IARC as human carcinogens. Generally, review and discussion of the epidemiological cancer literature related to benzene was limited due to the enormous amount of material needing to be covered since the last full monograph meeting on benzene in 1981, and because 32 other chemicals and occupations were also being evaluated. Moreover, among the 33 chemicals and occupations reviewed, there was some inconsistency in the use of studies for evaluating various cancers. In some situations, consideration could have been given to the inclusion of relevant unpublished, but readily available study results. Discussion and synthesis of the animal cancer studies and mechanistic data related to specific cancers also were limited. IARC's conclusion that there is sufficient evidence for benzene to cause acute non-lymphocytic leukemia only was based on an incomplete review. IARC should schedule another monographs meeting dedicated to a complete and full review and discussion of all potential cancers related to exposure to benzene and to benzene-containing mixtures. Am. J. Ind. Med. 54:157–164, 2011. © *2010 Wiley-Liss, Inc.*

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INTRODUCTION

In October of 2009, a Working Group (WG) selected by the International Agency for Research on Cancer (IARC) met in Lyon, France to evaluate the available evidence for cancer to humans for 33 ''chemical agents and related occupations.'' This Monograph 100 F meeting was the last of a series of Monograph 100 meetings to determine which site-specific cancers in humans are caused by agents or occupational processes previously categorized as ''human carcinogens'' in IARC Monographs 1-99. A summary of the Monograph 100 F evaluations is available [Baan et al., 2009]. Regarding

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benzene, the WG concluded there was sufficient evidence of carcinogenicity in humans for acute non-lymphocytic leukemia (ANLL) and limited evidence for acute lymphocytic leukemia (ALL) and for non-Hodgkin's lymphoma (NHL), including chronic lymphocytic leukemia (CLL) and multiple myeloma (MM).

IARC, however, was incomplete in its approach to benzene compared to the other chemical and occupational exposure evaluations. The major reason for this incompleteness was inherent in the otherwise useful approach to Monograph 100, an approach that differed from IARC's usual process by providing far less time for a thorough review and discussion of the literature for any single compound or occupation. IARC's procedure failed in the review of benzene because of the very long time period (28 years) since the previous benzene monograph, and the great interest in benzene that led to an enormous accumulation of relevant literature compared to the much smaller time-periods and more manageable literature for the other chemicals and occupational processes. Thus, it is not surprising that this time-limited difference in the ability to concentrate on the benzene literature led to an incomplete review and discussion of the epidemiological data and limited discussion and synthesis of the animal cancer studies and mechanistic data related to specific cancers associated with benzene exposure.

PROCEDURES OF THE IARC REVIEW

In order to evaluate the 33 designated chemicals or occupations, WG members were divided into four subgroups: one to evaluate the epidemiology of single chemicals; a second to evaluate the epidemiology of complex mixtures; a third to evaluate cancer findings from experimental animals; and a fourth to evaluate possible mechanisms through which the chemical agents and related occupations may cause specific cancers in humans. The subgroup related to mechanisms incorporated data from both epidemiological and experimental studies.

Having been a WG member for Monograph 100 C on metals and fibers which met in March 2009 [Straif et al., 2009], as well as earlier IARC Monograph meetings, I am familiar with the IARC Monograph review, evaluation and interpretation procedures. As part of the IARC process, WG members are asked to prepare topical drafts of their evaluations of the relevant available literature related to their area of expertise prior to the meeting, but IARC asks that the reviewers not draw conclusions on the evidence of carcinogenicity until the WG members thoroughly review the data as part of the meeting process. Prior to the meeting, WG members are usually assigned a chemical or occupational process for which they write a section that includes an evaluation of either the sources of exposure to the chemical, or epidemiological study results, or findings in experimental animals, or mechanisms related to specific cancers observed in humans depending upon the subgroup to which they are assigned. Thus, for each chemical the draft may have 4–5 separate authors, for example, one for each specific area of expertise. These summaries are then peer reviewed by other WG members and IARC staff according to their expertise and returned to the original authors for suggested revisions prior to the meeting. Thus, it is likely that a WG member arrives at the meeting with familiarity for at least two chemicals/processes, for example, the one he or she wrote and the one that he/she reviewed.

The familiarity of WG members with data for chemicals/processes beyond their primary assignments depends upon their knowledge of the toxicity of these chemicals based on their career activities prior to the meeting. It is unlikely, however, that WG members would be familiar with data within their area of expertise for all of the 33 chemicals/occupations prior to the meeting. It is also more than likely that most WG members would not be knowledgeable with most of the data not related to their particular area of expertise. For example, it is unlikely that those reviewing animal cancer data are proficient with epidemiological study results, or conversely that epidemiologists are well informed about many of the animal cancer or mechanistic study results. Since all WG members, regardless of expertise, vote on the degree of overall evidence for carcinogenicity to humans, for example, a chemist or exposure specialist has a vote equal to a toxicologist or an epidemiologist, it is important that sufficient time be allowed for a full discussion of the epidemiological, experimental animal findings and mechanistic study results as these three areas of toxicology all provide key information related to the interpretation of cancer risk to humans. A lack of full discussion of these areas of toxicology is likely to result in WG members voting on evidence of carcinogenicity while not being fully aware of the evidence outside of their area of expertise. This review became further complicated because the full WG must read summaries prepared during the week and vote on the levels of evidence and target sites for the 33 chemicals and occupations presented.

MAGNITUDE OF INFORMATION AVAILABLE ON THE CARCINOGENICITY ON BENZENE

The last IARC WG to consider the carcinogenicity data for benzene was held in 1981 and published in 1982 [IARC, 1982a]. IARC, as part of Supplement 7 [IARC, 1987], evaluated more than 100 chemicals previously reviewed, including benzene, but the review did not include an in-depth evaluation of the literature on these chemicals. Thus, review of benzene as part of the October 2009 Monograph 100 F required an extensive review of the literature since 1981. [Note: The mandate to the reviewers was to evaluate only

relevant articles that had been published since the 1987 Supplement, but even during this somewhat truncated period, a large, relevant literature was published.] In the past 28 years, based on the epidemiological literature alone, more than several hundred studies related to the risk of various cancers, other adverse effects on the bone marrow in relation to benzene exposure, and to products containing benzene have been published in the scientific literature. IARC [Baan et al., 2009] states that the WG reviewed more than 100 epidemiological studies related to benzene exposure. Although the authors of the benzene evaluation compiled a vast literature on benzene, the IARC website on which other WG members had access listed only about 40 published reports in relation to the epidemiological literature. Most of the key articles, however, were made available during the meeting in hard copy form to members of the WG for review. There was, however, limited time during the meeting to read and review such a large body of literature due to the necessity to evaluate and synthesize the literature for the other 32 chemicals or occupations. During the deliberations, several WG members commented that a new monograph meeting dedicated solely to benzene was needed as the task of evaluating the benzene literature was too great to be carried out in the format of the Monograph 100 meetings.

Evaluation of the benzene literature often requires reviews of earlier publications, or review of more detailed unpublished iterations of the same study population. For example, the unpublished Health Watch studies of Australian petroleum workers [Bisby et al., 1992, 1998; Gun et al., 2000, 2005; Sim et al., 2007] that have been available ''on-line'' provide important information for adequately evaluating the published versions of the successive cohort follow-up periods [Christie et al., 1991; Gun et al., 2004, 2006] in relation to exposure and response relationships as presented in the journal publications. [Note: I agree, in general, with the protocol for IARC Monographs that only allows consideration of articles published in the peer-reviewed literature; however, in some cases where evaluation of data in an unpublished report, especially when the detailed findings are readily available online, may shed more light on the published report, it may be important to review the unpublished reports as well. IARC, for instance, does include unpublished NTP Technical Reports and ATSDR Toxicological Profiles in its evaluations.]

A heroic effort was put into the WG's benzene epidemiology review. The benzene epidemiological literature related to cancer alone that was reviewed resulted in about 35 tables of data being presented initially to the two epidemiology subgroups, for example, the groups assigned primarily to single chemicals or to complex mixtures. Since most members of the WG, including the epidemiologists, are likely not to have reviewed the epidemiological data on benzene, it seems reasonable to assume that most members of the WG would have to rely on the evaluation and discussion of the literature provided by one or two of the epidemiologists. WG members also needed to consider the experimental animal toxicological findings and mechanistic study information. More time was devoted to the discussion of benzene than to any other carcinogenic agent, nonetheless, the amount of time available for actual discussion, however, was limited by time constraints and the need to keep on schedule in order to complete evaluations for the additional 32 chemicals and occupational exposure situations that required completion by the end of the meeting.

EXAMPLES OF DATA FOR SPECIFIC CANCERS NOT ADEQUATELY DISCUSSED

It is not my intention to rebut the evaluation of the IARC review on benzene, but rather to provide a few examples of how the time constraints on the benzene review resulted in an incomplete review and discussion of the data. In addition, there was an inconsistency in the selection of epidemiological studies that were considered as part of the benzene evaluation versus the studies selected by the WG for review of other chemicals and processes. As a result, some contradictory conclusions seem to have been reached with regard to the site-specific cancers related to benzene as compared to other chemicals or occupations. Several of these issues as presented below were raised during the meeting, but were not addressed by the WG.

Review of Data Related to Benzene and Acute Lymphocytic Leukemia (ALL)

ALL is primarily a leukemia of childhood. In the US, about 70% of the cases diagnosed annually are found among those under the age of 20 years. For adults, ALL comprises about 5% of the total number of leukemia cases diagnosed annually [Horner and Ries, 2006]. This demographic information suggests that environmental causes of ALL might best be evaluated through the study of childhood ALL in contrast to occupational cohort studies that were mostly used in the benzene review. A decision was reached by the epidemiology WG, however, to focus mostly upon occupational studies because environmental studies provided a more limited evaluation of exposure. Yet, one of the environmental studies of benzene and 1,3-butadiene exposure that showed a dose–response for both substances in relation to risk of childhood leukemia was not considered as part of the benzene evaluation, but was considered by the epidemiology WG in its 1,3-butadiene (BD) evaluation [Whitworth et al., 2008]. As a matter of process, the exclusion of the Whitworth et al. [2008] study as part of the benzene evaluation and inclusion of the study in the BD evaluation suggests an inconsistent process in the selection of types of studies to be reviewed.

Studies demonstrating significantly elevated risks of childhood ALL in relation to maternal exposure to benzene [Infante-Rivard et al., 2005], to gasoline [Shu et al., 1988], and to paints and thinners [Shu et al., 1999; Schuz et al., 2000; Freedman et al., 2001] also were not discussed as part of the benzene evaluation. Yet, gasoline, oil-based paints, and paint thinners contain benzene though the benzene content in the paints and thinners has, in general, been considerably reduced over time. Risk of hematopoietic cancers, including ALL, from benzene exposure to the general population from mobile and fixed sources also might have been considered if more time were available to the WG.

The WG also did not consider case reports of individuals with ''benzene poisoning,'' aplastic anemia or pancytopenia progressing to ALL [Delore and Borgomano, 1928; Falconer, 1933; Rejsek and Rejskova, 1955; Browning, 1965; Hernberg et al., 1966; Goguel et al., 1967; IARC, 1982a; Aksoy, 1988; Sole et al., 1990; Hernberg, undated]. Yet, historically, benzene was considered as a cause of AML (acute myelocytic, monocytic, and erythro-leukemia), not on the basis of epidemiological study, but rather on the basis of individuals with ''benzene poisoning,'' for example, mostly aplastic anemia or pancytopenia progressing to AML.

Review of Data Related to Benzene and Chronic Lymphocytic Leukemia (CLL)

IARC concluded there was limited evidence in humans that benzene could cause CLL. Yet, the WG concluded that there was sufficient evidence that employment in the rubber industry was causally associated with leukemia, of which most of the excess was due to CLL. These conclusions appear contradictory. None of the data points for leukemia related to rubber worker employment presented by the WG at the plenary session demonstrated a significant excess of leukemia. When this observation was pointed out by one of the WG members, the response was that the earlier studies from the 1982 review demonstrated significantly elevated risks of leukemia and that IARC had previously concluded that working in the rubber industry provided sufficient evidence for leukemia in humans. Upon review of IARC Monographs volume #28 [IARC, 1982b], the only specific type of leukemia mentioned is CLL as demonstrated in the University of North Carolina studies [McMichael, 1975]. IARC [1982b] pointed out this elevated risk of CLL and stated that benzene was used as a solvent in the rubber industry in the past and was likely still a contaminant in solvents at the time of the North Carolina studies, implying that benzene contamination of solvents may have been responsible for the elevated risk of CLL in these workers.

It is noteworthy that data for the rubber industry presented to the WG during the meeting indicated that the highest relative risk for leukemia was identified among those employed in the inner tube department of the Li and Yu [2002] study, OR = 7.8 (0.8–78.8) based on three deaths. Of these three deaths, two were from lymphatic leukemia and among the seven deaths from leukemia identified in the study overall, five were from lymphatic leukemia (sub-type not indicated). The authors of the study concluded that the excess of leukemia in the rubber industry was considered to be real and was attributed to exposure to solvents, particularly benzene [Li and Yu, 2002] and that results from more recent studies they reviewed tended to confirm this conclusion. Again, the association between rubber solvent exposure (contaminated with benzene) and risk of leukemia in the rubber industry appears to indicate a predominance of lymphatic leukemia, most of which has been identified as CLL. [Note: While BD can be a significant exposure in the rubber industry, it is not a contaminant of rubber solvents.]

In 1976, I was a member of the NIOSH Benzene Task Force that reviewed the available literature in order to update the NIOSH [1974] Criteria Document on Benzene. The primary epidemiological evidence at the time was provided from the study of rubber workers that demonstrated elevated risks of CLL, which NIOSH attributed to benzene contamination of the rubber solvents [NIOSH, 1977]. The Director of NIOSH [Finklea, 1976] pointed out to OSHA that recent epidemiological studies in the rubber industry linked chronic leukemia, for example, CLL to benzene exposure. Thus, both NIOSH [1977] and IARC [1982b], respectively, concluded that benzene in rubber solvents was, or likely was associated with the elevated risk of CLL in the rubber industry.

The 2009 WG's conclusion that there is limited evidence for benzene to cause CLL and sufficient evidence for employment in the rubber industry to cause leukemia—most of which has been identified to date as CLL or lymphatic leukemia in general is inconsistent in the 2009 IARC evaluation of benzene in relation to the other chemicals/occupations that it reviewed.

The WG also did not discuss the results from several additional studies that have a bearing on benzene exposure and risk of lymphatic leukemia. In these studies, risks were elevated for lymphatic leukemia in general or for CLL specifically [Girard and Revol, 1970; Schottenfeld et al., 1981; Rushton and Alderson, 1983; Wongsrichanalai et al., 1989].

Review of Data Related to Benzene and Multiple Myeloma (MM)

IARC concluded there was limited evidence for benzene to cause MM in humans. However, some published studies as well as unpublished studies that have a bearing on benzene exposure and risk of MM were not considered by the WG. For example, the WG considered the Kirkeleit et al. [2008] study of Norwegian crude oil-exposed workers as providing evidence of an association between benzene exposure and risk of MM, but it did not review an additional published

study of crude oil-exposed workers [Divine and Hartman, 2000] that demonstrated an elevated risk of MM. Nor did it consider a third study of crude oil exposed workers that demonstrates a significant association with MM (as well as AML and NHL), presumably because the study was not published in the peer-reviewed literature even though it had been completed by 1992 [Delzell et al., 1992] and is available. To date, only the results from this study related to risk of AML have been published [Saithiakumar et al., 1995] in a peer-reviewed journal.

Although IARC has a policy of not considering unpublished studies, the methodology of the Delzell et al. [1992] case-control study had been peer reviewed in the publication of the AML results [Saithiakumar et al., 1995]. Since identical methodology was used for establishing relative risk for MM, IARC may have had justification for including the study results for MM even though they were not presented, per se, in a journal. Therefore, two studies in addition to the Kirkeleit et al. [2008] study that indicate associations between exposure to crude oil, containing a range of 0.1–0.3% benzene, and death from MM (as well as from leukemia and NHL) were not considered in the WG evaluation of MM.

As mentioned earlier, only the published results of the follow-up studies of the cohort of Australian petroleum industry workers were considered by the WG. Again, we are presented with a situation where the methodology used in these cohort studies was peer-reviewed as three of the follow-up analyses were published in journals [Christie et al., 1991; Gun et al., 2004, 2006], while the analyses for two of the cohort follow-up periods demonstrating the highest risks for MM and AML were not published [Bisby et al., 1998; Gun et al., 2000]. An evaluation of the entire set of data that includes all six of the cohort follow-up periods, however, may have provided additional evidence of an association between benzene exposure and risk of MM.

Review of Data Related to Benzene and Non-Hodgkin's Lymphoma (NHL)

The IARC WG concluded there was limited evidence for benzene to cause NHL in humans. As pointed out in the WG's draft monograph on benzene, NHL is a heterogeneous group of diseases, whose classification has evolved over the last several decades. This has resulted in the categorization of different subtypes of NHL into different categories for separate statistical analyses in epidemiological studies. For example, in some studies of NHL, MM is analyzed as a separate entity, while in other studies it has been combined with NHL. In some studies, CLL, now considered a NHL along with MM, is categorized for analyses with leukemia and in other studies it is included with NHL. Thus, IARC needed to establish some guidance to the WG about whether an association between benzene exposure and CLL, or MM, provided evidence for benzene as a cause of NHL, or only as a cause of CLL or MM separately.

In fairness to the authors of the benzene epidemiology chapter, a tremendous effort was placed in abstracting data from approximately 30 cohort and 20 case–control studies related to NHL alone. Even without considering the benzene data related to other cancers, the NHL literature by itself constituted a vast amount of data that needed to be discussed during the WG meeting. Hence, it was not surprising that several WG members suggested that IARC consider a new benzene review as mentioned earlier.

With regard to a review of mechanistic information, relatively little time was spent on a discussion of the biological plausibility for benzene to cause NHL, including CLL and MM. The vast majority of the mechanistic section on benzene was devoted to acute leukemia. Yet, there is a considerable amount of relevant information that might have been considered related to the plausibility for benzene to cause B-cell malignancies in humans. Some of this literature includes a number of observations in humans [Greenburg, 1926; Hunter, 1939; Mallory et al., 1939; Vigliani and Saita, 1964; Aksoy et al., 1971; Vigliani, 1976; Aksoy and Erdem, 1978; Picciano, 1979; LeNoir and Claude, 1897; Aksoy, 1988; Hogstedt et al., 1991; Santos-Mello, 1992; Oesch et al., 1995; Nilsson et al., 1996; Ward et al., 1996; Infante, 2001; Qu et al., 2002; Sul et al., 2002; Mbulaiteye et al., 2003; Lan et al., 2004, 2006; Clifford et al., 2005; Theander et al., 2006] as well as in experimental animals [Snyder et al., 1980; Cronkite et al., 1984, 1985; Huff, 1986; Huff et al., 1989; Maltoni et al., 1989; Farris et al., 1993; Boley et al., 2000; NTP, 2007; Kawasaki et al., 2009].

RECOMMENDATIONS FOR THE CONDUCT OF A FUTURE WORKING GROUP MEETING ON BENZENE

For this proposed meeting, I recommend that:

(1) IARC focus solely on the carcinogenicity of benzene, including epidemiological and experimental evidence as well as information related to mechanisms and biological plausibility.
(2) IARC orient the epidemiology review by specific categories of benzene exposure. For example, studies might be assigned according to industrial exposures to benzene in petroleum production and refining operations, and to the transport of crude oil and other benzene products on both land and sea.
(3) IARC assure a complete review of the benzene literature by including exposure to benzene containing mixtures such as paints, paint products and solvents, and to rubber solvents. Another category of exposure for epidemiological study evaluation might include environmental

exposures to benzene from refineries and from other fixed sources, as well as from mobile sources related to gasoline exposure. An additional grouping might include exposure to gasoline at terminals, during transport and at petrol stations and also community exposures to gasoline from leaking underground gasoline storage tanks. (Certainly, other combinations of benzene exposure could be developed. The major concept should be the grouping of exposures in such a way that all benzene exposed populations are evaluated for risk of LHP cancers. These groupings then need to be assigned separately to WG members for review to better assure that all benzene exposed populations are evaluated for cancer risk.)

(4) IARC select industrial hygienists to the WG with particular experience in benzene exposures to facilitate the selection of populations and exposure patterns for evaluation.
(5) IARC select both clinical and experimental pathologists to the WG to assist in the evaluation of histological data related to LHP cancers so there is an appreciation of the relationship of the various LHP cancers to each other, as well as correlations between humans and experimental animals. (Changes in the diagnostic groupings of LHP cancers that have taken place over the past three decades need to be considered in the evaluation.)
(6) IARC devote sufficient amounts of time for a discussion of the epidemiological findings as well as the biological plausibility and mechanistic findings in relation to benzene exposure and the various LHP cancers.
(7) IARC consider review of unpublished reports in situations where they can assist in interpretation of the published versions of the same study populations.
(8) IARC review of benzene not be held until the draft evaluations are completed and reviewed by IARC and other WG members.

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