

**COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD,
CONSUMER PRODUCTS AND THE ENVIRONMENT****IS AGE AN INDEPENDENT RISK FACTOR FOR CHEMICALLY INDUCED
ACUTE MYELOGENOUS LEUKEMIA IN CHILDREN?****INTRODUCTION**

1. There have been suggestions that young age is a risk factor for some forms of cancer. This is reflected in the US EPA's Cancer Risk Assessment Guidance, which assumes, as a default, that children are inherently up to 10-fold more sensitive than adults to genotoxic carcinogens. When the COC last discussed this issue in July 2006, Members considered that there was insufficient evidence at this stage to adopt adjustment factors for genotoxic carcinogens for different life stages.

2. In a recent review by Pyatt et al (2007) (attached), this assumption was tested in children receiving treatment with high dose chemotherapy and/or radiation and the development of secondary or therapy-related acute myelogenous leukemia (t-AML). t-AML is well established as a potential long-term consequence of exposure to such treatment. In their review, Pyatt et al (2007) investigated the effect of age at treatment on a child's susceptibility to developing therapy related AML.

2. Data used for this study were obtained from available, published literature. Literature searches of PubMed were conducted using one or more of the following terms in various combinations: secondary malignant neoplasm (SMN), childhood cancer, adolescents, secondary malignancy, Hodgkin's disease (HD), second cancer, pediatric Hodgkin's disease, t-AML, acute lymphocytic leukemia, ALL. The authors identified 435 citations, of which 220 were reviewed based on relevance as determined from the published abstract. Of these, 27 studies were critically reviewed as they were found to contain data that specifically addressed the age of the patient as it pertained to the risk of chemically induced leukemia. The literature on the treatment of pediatric HD was used primarily to evaluate whether patient age was an independent risk factor for developing t-AML following treatment with alkylating agents and the clinical literature on the therapeutic management of childhood ALL was used to evaluate the effects of age on the risks of t-AML associated with treatment with topoisomerase reactive drugs. For the purposes of this paper, the terms acute nonlymphocytic leukemia (ANLL) and acute myelogenous leukemia (AML) are used interchangeably.

3. The paper noted that risks of t-AML associated with chemotherapy were calculated and reported in a variety of ways in the published literature, with some using standard incidence ratios (SIR), actuarial risks, relative risks (RR), absolute excess risks (AER), and cumulative risks. Others estimated the number of cancer cases expected by using general cancer incidence rates from various cancer registries such as SEER, the Third National Survey from the NCI or local registries, specific for each region and multiplied by the accumulated person-years at risk. Other groups calculated the

expected number of cancers based on age, gender and period specific incidence rates for the general population.

4. The paper discusses the use of alkylating agents in the treatment of primary malignancies and their capabilities in producing myelodysplastic syndrome and/or acute myelogenous leukemia. The paper also discusses the difficulty in discerning the offending agent as modern therapeutic regimens utilise a combination of drugs. According to the authors, as a class, there is little doubt that treatment with these drugs alone or in various “cocktails” increase the risk of developing t-AML. One notable observation from morphological and cytogenetic analysis of AML arising secondarily to treatment with alkylating agents is the involvement of recognisable cytogenetic lesions, specifically the loss of part or all of chromosome 7 and/or 5. The paper also discusses the use of topoisomerase inhibitors in the treatment of primary malignancies, their primary target topoisomerase II, an enzyme required for DNA replication, and their ability to cause secondary AML.

5. Tables 2 and 3 in the attached paper summarise the findings of the major studies which evaluated the risk of t-AML or t-ANLL following treatment for paediatric Hodgkin’s Disease (HD) or HD among paediatric and adult patients. The authors noted that many of the available studies present data for relatively few cases of t-AML, limiting the statistical power of these studies to detect clear trends in age, but also note? how as a group the assessment of the studies is informative in assessing patterns of risk with age at treatment. Table 1 focuses on t-AML following treatment for HD in exclusively paediatric populations where most studies report fewer than 20 total cases of t-AML. The paper found that these studies were fairly consistent in concluding that younger children were either at similar or lower risk of t-AML following treatment for HD compared to older children.

6. Four studies (Meadows et al. (1989); Jenkin et al (1996); Wolden et al (1998) and Van Leeuwen et al (2000)) presented noagespecific rate data, but conducted statistical analyses or made observations regarding the impact of age at treatment on risk. Meadows et al. (1989) concluded that age was not a determining factor in a patient’s risk of developing t-AML. Jenkin et al. (1996) found that age (younger or older than 14 years) was not correlated with the risk of developing any type of secondary malignancy, including secondary leukemia. In Wolden et al (1998), although age-specific data on secondary leukemia was not presented, the authors concluded that age at Hodgkin’s Disease treatment did not impact on risk of any second neoplasm. Van Leeuwen et al (2000) found no consistent pattern of risk with age at treatment for HD, contrasted with the significant increase in risk for solid tumours observed in younger patients compared to older patients.

7. The remaining studies present explicit data on leukemia occurrence by age categories. In the smaller studies of Pui et al (1990), Beaty et al (1995) and Sankila et al. (1996), no leukemia cases were observed among the youngest paediatric age group category in each study. Pui et al reported no cases of t-AML following HD treatment in children ages 0-12 years; in contrast, 2% of older patients developed t-AML following therapy with MOPP. Independent assessment of the same dataset by Wegelius (1992) and Levine and Bloomfield (1992) came to the same conclusions, that younger children (>12 years) did not develop t-AML and were at a relatively lesser risk than older children. In a small study, Beaty et al (1995) investigated the

risk of developing t-ANLL and other secondary malignancies in younger patients (n=114) and in patients older (n=385) than 10 years old. The authors observed only four cases of t-ANLL in the study, all occurring in the older age group. They also reported that the younger age group had less risk for developing t-ANLL, but a higher risk of developing solid secondary tumours. Sankila et al. (1996) evaluated secondary malignancies in 1641 paediatric patients, grouped into age categories of 0-4, 5-9, 10-14, and 15-19 yrs. The age-adjusted incidence rates (SIR) were reported in the study to be NA, 18, 46 and 8 for secondary leukemias in the age groups, respectively.

8. The two largest studies of exclusively pediatric populations, by Bhatia et al. (2003) and Metayer et al. (2000), came to opposite conclusions regarding the pattern of risk with age of treatment among pediatric patients. Bhatia et al. (2003) evaluated secondary malignancies in pediatric HD patients as a follow up study to the report of Meadows et al. (1989). The cohort included 1380 patients with 27 secondary leukemias. The patients were divided into three age brackets of 0-5, 6-9 and 10-16 years. The authors reported a synergistic relationship between chemotherapy and radiation therapy in the induction of secondary leukemias. The RRs of developing secondary leukaemia among the younger age groups compared to the oldest age group were less than 1.0 but were not statistically significantly different from 1.0. Metayer et al. (2000) conducted a study evaluating secondary malignancies in 5925 HD patients under the age of 21 from multiple cancer centres and countries. This study reported that the AER of secondary acute leukaemia in pediatric HD patients ages 0-9, 10-16 and 17-20 was 10 (95% CI 16.9 -100.8), 7 (95% CI 22.5 -69.1) and 2 (95% CI 4.6-27.3), respectively.

9. Numerous studies have been conducted that combine pediatric and adult cases of HD or adult cases over a broad range of ages. Of these studies, most report actuarial risks or AERs for the pediatric age group lower than or similar to those for young adults. Mauch et al. (1996) reported the AER for secondary leukaemia in both pediatric and adult HD patients. The AER for secondary leukaemia in patient groups segregated into 3 age groups of <16, 17-39 and >40 years were 5.4, 6.9 and 30.1 respectively. However, after adjusting for the age-dependent expected rates of leukemia, the RRs for secondary leukemia were not affected by age. In this study the use of radiation therapy in combination with chemotherapy did not increase the risk of developing leukemia over chemotherapy alone. In contrast, Mauch et al. (1996) reported that the risk for secondary breast cancer was markedly age dependent and that younger girls less than 15 had a much higher RR and AER than older girls or adults. In a large study, Boivin et al. (1995) reported 122 cases (116 occurred in the first 14 yrs of follow up) of secondary leukemias from a cohort of 10,472 patients from 14 cancer centres in the US and Canada. They concluded that pediatric patients age 15 or younger demonstrated risks of secondary leukemia similar to those in the young adult and older adult patient. Valagussa et al. (1985) reported that the actuarial risk of developing t-ANLL following treatment for HD was 0.6% for patients under 17, 2.7% for patients aged 17-20 and 7% for patients over 40 years in 1329 pediatric and adult HD patients. Swerdlow et al. (1993) also evaluated the relationship between the age of the patient and the associated risk of t-AML. They reported a statistically significant increase in RR with increasing age, but no statistically significant relationship between age and AER. In a study of HD patients by Coleman et al. (1982), actuarial risk of secondary leukemia was 1.3 for <20 years, 3.8 for 20-29 yrs, 3.6 for 30-39 yrs, 3.5 for 40-49 yrs and 12.7 for >49 yrs. Similar results were obtained

by Dores et al. (2002). In this study, HD patients were segregated into ages of <21, 21-30, 31-40 and 41-50. The AER rose progressively with increasing age (3.6, 4.2, 7.2, and 10.6, respectively).

10. A few studies report that assessments of relative risk as a metric show higher relative risks for younger patients compared to older ones (Kaldor et al., 1990; Dores et al., 2002 and Swerdlow et al., 1993). Kaldor et al. (1990) reported that HD patients younger than 38 has a higher relative risk of t-AML compared to patients over 38. However, this difference was attributed in part to the low background incidence rates in younger adults compared to older adults, leading to a high relative risk based on a few cases. Swerdlow and Dores also evaluated the relationship between age and the associated risk of t-AML both in terms of relative risk and AER. In both studies, the authors reported a statistically significant decrease in relative risk with increasing age but either no statistically significant relationship between age and AER or a statistically significant elevation in AER association with increasing age (Swerdlow et al., 1993; Dores et al., 2002)

11. Other investigators have evaluated the risk of developing secondary t-AML in children treated for acute lymphoblastic leukemia (ALL). Pui et al. (1989) reported 13 cases of t-AML developed out of 733 treated patients and 12 of these cases arose from children treated with epipodophyllotoxins. These investigators evaluated children aged 2-9 and 10 or older and concluded that there was no risk of developing t-AML in children treated for ALL. Lonig et al. (2000) evaluated the effect of age on ALL patients and risk of t-AML. The patients were divided into two groups and the authors reported no age-related differences in secondary leukemia risk in the study. Winick et al. (1993) evaluated the risk of developing t-AML in children treated with etoposide (and other drugs) for ALL. There were 10 cases of therapy related AML or MDS (myelodysplastic syndrome) reported out of 205 treated children. The actual incidence of t-AML/MDS was 1%, 6%, 6% and 6% for the age groups <3, 3.0-4.4, 4.4-7.5, and >7.5 yr old, respectively.

12. Other studies have been conducted to investigate other primary childhood cancers and t-AML. Neglia et al. (2001) evaluated patient age at time of diagnosis of multiple childhood cancers (mostly solid tumours) and the risk of t-AML. In this study, patients were segregated into ages of 0-4, 5-9, 10-14, and >15 yr of age at time of diagnosis. There was a statistically non significant increase in RR compared to the youngest age group for the other three age groups (1.89, 1.85, 1.41 respectively). In contrast, Neglia et al. (2001) reported that younger age correlated well with increased risk of developing solid tumours (breast, CNS and thyroid). Olsen et al. (1993) did not find a correlation between development of secondary leukemias and the treatment of primary childhood cancers of various types. Tucker et al. (1987) reported that the AER of secondary leukemias following MOPP treatment in 9170 pediatric patients rose progressively with age (AER of 2.6, 4.0, 6.5 for age groups 0-4, 5-9, 10-14 yr). However, after adjusting for dose of drug, there was no statistically significant difference between those younger or older than 10 yr.

13. The paper also discusses the relevance of their findings that children do not appear to be especially susceptible to development of t-AML after exposure to chemotherapeutic agents for understanding potential susceptibility to developing cancer from exposure to environmental contaminants such as benzene. Chronic, high-

dose exposure to benzene has been established as an etiological agent in the development of AML in the adult population (Snyder, 2000; Kacew and Lemarie, 2000). While supportive evidence linking benzene and AML only exists in highly exposed occupational settings, there is speculation that sensitive populations exist (i.e. children). The paper suggests that, in the absence of benzene specific data for children, the clinical literature reporting t-AML in children treated with leukemogenic agents represents an available source of data to address this hypothesis. Similarities between chemotherapy and benzene-induced AML are available for disease type, cytogenetic lesions, disease progression and prognosis as reported in many molecular studies, case reports and epidemiological evaluations. Therefore, the authors consider that it is reasonable to assume that chemotherapy-induced AML represents an appropriate model for benzene induced AML and by extension to assume that children will not be at an increased risk of developing leukemia due to exposure to benzene compared to adults.

14. Overall, the pattern of results from the studies on t-AML in pediatric and combined pediatric and adult HD patients does not suggest an increase in risk of t-AML associated with treatment for HD in children compared to adults nor in younger children compared to older children. Only one study (Metayer et al., 2000) reported a decrease in risk with increasing age, while the majority reported a stable or higher risk of t-AML development with increasing age of the patient. Most of the studies that have examined age as a risk factor for t-AML induction indicate that patients older than 40 at treatment have an increased risk when compared to younger patients, with a similar pattern apparent in the general background incidence rates for AML. A recent paper by Rossi et al. (2005) suggests that an age-related shift in hematopoietic progenitor cell (HPC) “predisposition” might explain the increased risk of both t-AML and de novo AML observed in older patients. It should also be noted that many of the studies reviewed by Pyatt et al. (2007) clearly illustrate that chemotherapy-induced leukemia in children (from both classes of therapy) follows a predictable dose-response, with higher risks associated with increasing cumulative doses. To conclude, the paper acknowledges that haematopoietic and immunological differences exist between adults and children but suggest that there is no evidence that a younger age increases an individual’s susceptibility to chemically induced leukemogenesis.

Questions for the committee

1. What are members’ views on this paper?
2. Do the members’ agree with the conclusions drawn by the authors?
3. What are members’ views on the use of the data from chemotherapeutic-induced AML literature to address the hypothesis that a sensitive population (children) might exist to benzene-induced AML?

COC Secretariat, September 2008

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