DRAFT - DO NOT CITE OR QUOTE

EPA/600/R-10/095A
September 2010
External Review Draft

Lymphohematopoietic Cancers Induced by Chemicals and Other Agents: Overview and Implications for Risk Assessment

NOTICE

THIS DOCUMENT IS AN EXTERNAL REVIEW DRAFT. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency Policy. It is being circulated for comment on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

DISCLAIMER

This document is a preliminary draft for review purposes only. This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the EPA. It does not represent and should not be construed to represent any Agency determination or policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

ABSTRACT

The objective of this report is to provide an overview of the types and mechanisms underlying the lymphohematopoietic cancers induced by chemical agents and radiation in humans, with a primary emphasis on leukemia and leukemia-inducing agents. Following a brief discussion of hematopoiesis and leukemogenesis, a review of the major classes of leukemia-inducing agents—radiation, chemotherapeutic alkylating agents, and topoisomerase II inhibitors—is presented along with information on the mechanisms by which these leukemias occur. This information is then compared with similar information for selected environmental and occupational leukemia-inducing agents. The last section focuses on how mechanistic information on human leukemia-inducing agents can be used to better inform risk assessment decisions. It is evident that there are different types of leukemia-inducing agents that act through different mechanisms. Even though most have a mutagenic mode of action, leukemia-inducing agents have different potencies and associated risks, which appear to be significantly influenced by the specific mechanisms involved in leukemogenesis. Identifying the specific types of cancer-causing agents with their associated mechanisms and using this information to inform key steps in the risk assessment process remains one of the ongoing challenges for research and regulatory scientists.

CONTENTS

LIST OF TABLES v
LIST OF FIGURES vi
LIST OF ABBREVIATIONS vii
PREFACE viii
AUTHORS, CONTRIBUTORS, AND REVIEWERS ix
EXECUTIVE SUMMARY xi

1. INTRODUCTION TO LYMPHOHEMATOPOIETIC CANCERS 1
   1.1. OVERALL INCIDENCE AND TRENDS 3

2. HEMATOPOIESIS 5

3. ORIGINS OF LYMPHOHEMATOPOIETIC NEOPLASIA 8

4. LEUKEMIA- AND LYMPHOMA-INDUCING AGENTS 11

5. OVERVIEW OF THE MAJOR CLASSES OF LEUKEMIA-INDUCING AGENTS 13
   5.1. IONIZING RADIATION 13
   5.2. CHEMOTHERAPEUTIC AGENTS 14
      5.2.1. Alkylating Agent-Related Leukemias 15
      5.2.2. Topoisomerase II Inhibitor-Related Leukemias 16
      5.2.3. Other Likely Leukemia-Inducing Therapeutic Agents 19

6. MECHANISMS INVOLVED IN t-AML 21

7. FACTORS CONFERRING AN INCREASED RISK OF INDUCED LEUKEMIA 24
   7.1. MYELOSUPPRESSION AND IMMUNOTOXICITY 24
   7.2. GENETIC POLYMORPHISMS 25

8. EXAMPLES OF SPECIFIC LEUKEMIA-INDUCING CHEMICALS 29
   8.1. MELPHALAN 29
   8.2. ETHYLENE OXIDE 30
   8.3. 1,3-BUTADIENE 32
   8.4. FORMALDEHYDE 35

9. RISK ASSESSMENT IMPLICATIONS 37
   9.1. HAZARD IDENTIFICATION 37
      9.1.1. Utility of Short-Term Genotoxicity Tests 38
      9.1.2. Usefulness of Animal Bioassays 39
      9.1.3. Combining Different Types of Lymphohematopoietic Cancers for Analysis ... 40

CONTENTS (continued)

9.1.4. Potential Influence of Latency Period in Identifying Leukemogens 42
9.1.5. Metabolism and Bioactive Dose at the Target Organ 43
9.1.6. DNA-Adduct Type, Metabolism, and Repair 44
9.1.7. Individual Susceptibility 45
9.1.8. Summary 46

REFERENCES 70

LIST OF TABLES

Table 1. Simplified classification of the major lymphohematopoietic neoplastic diseases in humans based largely on the French-American-British (FAB) classification 47

Table 2. WHO classification of myeloid and related neoplasms 49

Table 3. WHO classification of lymphoid neoplasms..... 51

Table 4. Cytogenetic comparisons of *de novo* leukemias and t-AML 54

Table 5. Frequency of molecular mutations in *de novo*AMLand t-MDS/t-AML 56

Table 6. Gene mutations observed in the Copenhagen series of 140 patients with t-MDS (*n* = 89) or t-AML (*n* = 51)..... 57

Table 7. Characteristics of selected known and probable human leukemia- and lymphoma-inducing agents..... 58

Table 8. Likely mechanisms involved in the carcinogenesis of selected known and probable human leukemia- and lymphoma-inducing agents..... 61

Table 9. General characteristics of human leukemias and related neoplasms induced by recognized leukemia-inducing agents 66

LIST OF FIGURES

Figure 1. Simplified model of hematopoiesis showing lineages of major types of hematopoietic cells. 67

Figure 2. Hierarchical stem cell origins of leukemia and related cancers 68

Figure 3. Genetic pathways of t-MDS and t-AML based on 140 cases from the Copenhagen study group. 69

LIST OF ABBREVIATIONS

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANLL	acute nonlymphocytic leukemias
BEIR	Biological Effects of Ionizing Radiation
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
EMS	ethyl methane sulfonate
ENU	*N*-nitroso-*N*-ethylurea
FAB	French-American-British
IARC	International Agency for Research on Cancer
MDS	myelodysplastic syndromes
MM	multiple myeloma
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
NQO1	NADPH quinone oxidoreductase 1
SCE	sister chromatid exchange
SEER	Surveillance Epidemiology and End Results
t-AML	karyotypes of patients who have developed leukemia following therapy
TMPT	thiopurine methyltransferase
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
WHO	World Health Organization

PREFACE

This report represents the update and expansion of two earlier U.S. Environmental Protection Agency (EPA) documents entitled "Chemical and Radiation Leukemogenesis in Humans and Rodents and the Value of Rodent Models for Assessing Risks of Lymphohematopoietic Cancers" (EPA/600/R-97/090, May 1997). This report provides an overview of chemically-induced leukemias and lymphomas and is intended to provide insights into how mechanistic information on leukemia-inducing agents can be used to assess risks from leukemia-inducing agents.

AUTHORS, CONTRIBUTORS, AND REVIEWERS

PROJECT MANAGER AND CONTRIBUTORS

Nagalakshmi Keshava, Ph.D.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

Babasaheb Sonawane, Ph.D.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

AUTHOR

David A. Eastmond, Ph.D.
University of California, Riverside
Riverside, CA 92507

REVIEWERS

George Woodall, Ph.D.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC

Maureen Gwinn, Ph.D.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

Glinda Cooper, Ph.D.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

AUTHORS, CONTRIBUTORS, AND REVIEWERS (continued)

Jennifer Jinot, Ph.D.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

Cheryl Scott, M.S.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

Chao Chen, Ph.D.
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

EXECUTIVE SUMMARY

Lymphohematopoietic neoplasias represent a heterogeneous group of clonal hematopoietic and lymphoid cell disorders and are one of the most common types of cancer induced by environmental and therapeutic agents. The objective of this report is to provide an overview of the types and mechanisms underlying the lymphohematopoietic cancers induced by chemical agents and radiation in humans, with a primary emphasis on leukemia and leukemia-inducing agents. Following a brief discussion of hematopoiesis and leukemogenesis, a review of the major classes of leukemia-inducing agents—radiation, chemotherapeutic alkylating agents, and topoisomerase II inhibitors—is presented along with information on the mechanisms by which these leukemias occur. This information is then compared with similar information for selected environmental and occupational leukemia-inducing agents. The last section focuses on how mechanistic information on human leukemia-inducing agents can be used to better inform risk assessment decisions. A brief overview of the major points in the report is presented below.

It is widely recognized that lymphohematopoietic neoplasms originate through multi-step processes involving a series of genetic and epigenetic alterations that transform a normal hematopoietic or lymphoid cell into a malignant tumor. The various lymphohematopoietic cancers are believed to originate in specific types of pluripotent or lineage restricted cells at different stages in hematopoiesis and immune cell development. Current evidence indicates that the acute and chronic myeloid leukemias (CMLs) as well as precursor lymphomas, the acute lymphoblastic leukemias (ALL) – B lymphoblastic leukemia/lymphoma and T lymphoblastic leukemia/lymphoma originate in hematopoietic stem or progenitor cells; whereas, other lymphomas and chronic lymphocytic leukemia (CLL) have their origins in mature lymphoid cells. This information on the origin of these cancers as well as morphologic, cytochemical and immunophenotypic features of the neoplastic cells provide valuable information for grouping various lymphohematopoietic cancers and for identifying the cell types targeted by carcinogenic agents.

Lymphohematopoietic neoplasia represents one of the most common cancers induced by chemical, physical, and infectious agents. To date, the International Agency for Research on Cancer (IARC) has identified over 100 agents as human carcinogens. Of these, approximately 25% have been shown to induce either leukemias or lymphomas in humans. Many of these are antineoplastic drugs, but

a variety of other agents including industrial chemicals, various forms of radiation, immunosuppressive drugs, and infectious agents have also been shown to induce lymphohematopoietic cancers in humans. In evaluating the different types of induced leukemias and lymphomas, a number of general patterns become apparent. Leukemias are the primary type of cancer induced by chemical agents. Most of these are acute nonlymphocytic leukemias (ANLLs, synonymous with acute myeloid leukemia [AML]) with relatively short median latency periods and are formed through the induction of mutations affecting critical cancer-related genes. Radiation, which is also thought to act through a mutagenic mode of action, is frequently associated with ANLL as well as CML and ALL.

Exposure to a variety of infectious agents is causally related to the formation of lymphoid neoplasms. The induced lymphomas identified to date appear to be primarily associated with chronic infection with either viruses or *Helicobacter* bacteria, agents that are immunomodulating, and/or specifically target lymphoid cells. Two chemical agents, cyclosporine and azathioprine, which are associated with the development of non-Hodgkin lymphoma (NHL) are also strongly immunosuppressive, and this immunosuppression is believed to play a critical role in the development of the associated lymphomas.

Among the induced leukemias, different subtypes with particular characteristics have shown to be induced by different classes of agents. For example, the alkylating agent class of chemotherapeutic agents typically induces acute myeloblastic leukemias that are often preceded by a myelodysplastic phase and are characterized by loss of all or part of chromosomes 5 or 7. These leukemias generally develop with a median latency period of 5–7 years from the beginning of treatment. In contrast, the leukemias induced by the epipodophyllotoxin class of topoisomerase II inhibitors develop much sooner with a median latency period of 2–3 years. These leukemias are typically characterized as monocytic or myelomonocytic subtypes and exhibit reciprocal translocations involving a specific region on the long arm of chromosome 11 (11q23). While much less is known about leukemias and lymphomas induced by environmental agents such as ethylene oxide and 1,3-butadiene, the types of neoplasms causally associated with these agents appear to differ substantially from those described above and suggest that these agents belong to a separate class of carcinogenic agent.

The last section of the report discusses how mechanistic information on human leukemia-inducing agents can be used to better assess the risks from exposure to environmental chemicals. A range of topics is considered including brief discussions on the usefulness of short-term and

animal bioassays, the combining of various tumor types for analysis, the impact of latency periods on the detection of leukemias, and the modifying influences of metabolism, pharmacokinetics, DNA-adduct type and repair, as well as individual susceptibility factors in assessing the risks associated with leukemia-inducing agents

In conclusion, it is evident that there are different types of leukemia-inducing agents that act through different mechanisms. Even though most have a mutagenic mode of action, leukemia-inducing agents have different potencies and associated risks, which appear to be significantly influenced by the specific mechanisms involved in leukemogenesis. Identifying the specific types of cancer-causing agents with their associated mechanisms and using this information to inform key steps in the risk assessment process remains one of the ongoing challenges for research and regulatory scientists. For the alkylating agent class of carcinogens, an approach such as that described by Vogel and colleagues (Vogel et al., 1998) supplemented with more recent genomic, proteomic, and biomarker information would appear to present a reasonable and scientifically valid step towards this objective.

1. INTRODUCTION TO LYMPHOHEMATOPOIETIC CANCERS

Lymphohematopoietic neoplasia can be described as an uncontrolled proliferation or expansion of hematopoietic and lymphoid cells that are unable to differentiate normally to form mature blood cells (Sawyerset al., 1991). These neoplasms represent clonal expansions of hematopoietic cells, almost always within either the myeloid or lymphoid lineage (Nowell, 1991; WHO, 2008). Infrequently, some leukemias exhibit both myeloid and lymphoid characteristics and are known as biphenotypic leukemias (Russell, 1997). The myeloid clones are designated as chronic or acute leukemias, depending upon the rate of clonal expansion and the stage of differentiation that dominates the leukemic clone. Lymphoid neoplasms typically manifest themselves in the blood as chronic or acute lymphoblastic leukemias or remain confined to lymphoid proliferative sites such as the lymph nodes or spleen and are designated as lymphomas (Nowell, 1991). Acute leukemias tend to have a rapid onset with a predominance of immature cells whereas chronic leukemias have a more insidious onset and progress over a period of months or years to a blast or acute leukemic phase.

Using this basic classification, leukemias can be described as one of four major types—acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphoblastic leukemia (CLL), and chronic myeloid leukemia (CML). Similarly, lymphomas are broadly classified as Hodgkin or non-Hodgkin lymphomas (NHL) depending upon the appearance of a specific cancer cell type, the Reed-Sternberg cell, which is found in Hodgkin lymphomas (ACS, 2009). Within these larger groupings, there are numerous subtypes involving specific cells that have unique characteristics, origins, and increasingly recognized clinical significance. These subtypes are generally classified according to morphologic, cytogenetic, immunophenotypic, and more recently, molecular characteristics according to the French-American-British (FAB) or World Health Organization (WHO) classification systems (Head and Pui, 1999; WHO, 2001, 2008; Haferlachet al., 2005). For convenience, a simplified classification scheme for the leukemias and lymphomas based largely on the FAB classification system (shown in Table 1 [Sullivan, 1993]) will be the basis for most descriptions used in this document. A more thorough and complicated classification of the primary types and subtypes of lymphohematopoietic diseases based on the most recent WHO classification (WHO, 2008; Vardiman et al., 2009) is shown in Tables 2 and 3 for myeloid and lymphoid neoplasms, respectively. It should be noted

that in the more recent WHO classifications (IARC, 2008c), lymphocytic leukemias and lymphomas are no longer considered to be different diseases and should be evaluated accordingly. However, for simplicity and due to the difficulties involved in reclassifying neoplasms based on studies that were conducted many years ago, the classifications used in the original studies or in the IARC monographs will be used in this document. It should be recognized, however, that considerable heterogeneity exists among NHL subtypes as classified according to older classification systems (Morton et al., 2007). In addition, the older schemes do not consider temporal changes in classifying distinct variants of NHL. For example, lymphomas of mucosa-associated lymphoid tissues (MALT) and mantle cell lymphoma as classified by WHO (2008), were previously considered as either pseudolymphomas or benign lympoid disorders. Similarly, some forms of T-cell lymphomas and aplastic large-cell lymphomas were earlier classified as Hodgkin's disease (Banks, 1992)

Among the leukemias, the two major diagnostic categories, ALL and AML, can be further classified based upon cellular features. ALL is subdivided by FAB morphology (L1, L2, and L3) and by immunophenotype (B-cell, early pre-B, pre-B, and T-cell) (Bhatiaet al., 1999). AML is classified primarily by morphological characteristics into eight different FAB subgroups (M0–M7) based upon the myeloid lineage and degree of maturation involved. Similarly, the myelodysplastic syndromes (MDSs), a series of blood disorders characterized by maturation defects resulting in ineffective hematopoiesis, have also been classified by the FAB and WHO systems (see Tables 1 and 2, respectively). These are commonly considered to be preleukemic because a variable, but significant, proportion (1 to 33%) of the various disorders progress to frank leukemia (Wright, 1995; WHO, 2001, 2008; Hasleet al., 2003).

The objective of this article is to provide an overview of the types of lymphohematopoietic neoplasia induced by chemical agents and radiation in humans, and to summarize current information on the mechanisms of chemical leukemogenesis. Much of the discussion focuses on myeloid neoplasms due to the evolving knowledge of lymphomas that is only now integrated into ongoing epidemiological and clinical studies. An overview of the major classes of leukemia-inducing agents—radiation, the alkylating agents, and topoisomerase II inhibitors—will then be presented followed by examples of environmental and occupational leukemia-inducing agents and a brief discussion of factors influencing chemical leukemogenesis. Lastly, the article will end with a discussion of how mechanistic information on human

leukemia-inducing agents can be used to better assess the risks from exposure to environmental chemicals.

1.1. OVERALL INCIDENCE AND TRENDS

Lymphohematopoietic neoplasms are an uncommon, yet significant, cause of cancer-related deaths. In 2009, it was estimated that leukemia would be diagnosed in 44,790 people in the United States (ACS, 2009). Slightly over half of these will be chronic leukemias (20,540) with the remainder being acute leukemias (18,570) and others that have not been clearly identified (5,680). Because of the limitations of current therapies, leukemia represents the 5th leading cause of cancer deaths among males in the United States and the 7th leading cause among females (ACS, 2009). Furthermore, it was estimated that 74,490 new cases of lymphoma would be diagnosed in the United States in 2009 (ACS, 2009). Of these, 89% (65,980 cases) were estimated to have been NHL and 11% Hodgkin lymphoma (8,510 cases). NHL represents the 9th leading cause of cancer-related deaths in males and the 6th in females. It should be noted that more recent cancer incidence and mortality data can be obtained from the National Cancer Institute (NCI)'s Surveillance Epidemiology and End Results (SEER) Web site (http://seer.cancer.gov/statistics/).

While leukemia occurs much more commonly in adults than in children, childhood leukemia still accounts for approximately 30% of all childhood cancers in the United States and is a leading cause of disease-related death among children (Smithet al., 2005; ACS, 2006). The incidence of leukemia in children (36 per million) is similar to that seen in young to middle-aged adults (ages 20−44) but roughly one-tenth of that of adults aged 45 years and older, where the annual incidences increase with age from 144 to 545 per million (Xieet al., 2003; ACS, 2006). In adults, roughly 85% of the leukemias are myeloid in origin with the remainder being lymphoid (Greaves, 1999). In children, the opposite occurs with 80% of the leukemias originating from lymphoid cells. Moreover, the incidence trends for adult and pediatric leukemias differ substantially. While the overall trend for adult leukemia has generally declined with time, the incidence of childhood leukemias has increased noticeably in recent years, largely due to an increase of ALL and AML in children that has increased by 1.1 and 0.5% per year, respectively (Xieet al., 2003). Similar increases have been seen across Europe and in other developed countries (Hrusaket al., 2002; Steliarova-Foucheret al., 2004). Fortunately, there has

been significant progress in treating childhood leukemias so that the 5-year survival rate for the affected children is now approximately 80% (ACS, 2006). The survival rate for adult leukemias varies by type with 5-year survival rates of 22% for AML patients, 66% for ALL patients, and 76% for CLL patients (ACS, 2009).

2. HEMATOPOIESIS

Hematopoiesis is the process by which the cells of the blood are formed. The development of the hematopoietic system begins in several mesodermal lineages in the mammalian conceptus with cells migrating from the primitive streak to three blood-forming tissues: the yolk sac, the para-aortic splanchnopleura/aora-gonadal-mesonephros region, and the chorio-allantoic placenta (for review, see Dzierzak and Speck [2008]). Hematopoietic stem cells capable of conferring complete long-term and multi-lineage repopulation of hematopoiesis in irradiated adult recipient mice appear in the aorta-gonadal-mesonephros and other tissues during the middle of embryogenesis (Embryonic Day 10.5 in the mouse). These cells proceed to colonize the liver, then the thymus, spleen, and bone marrow (by Embryonic Day 15 in the mouse) where hematopoiesis primarily occurs after birth.

The formation of blood cells originates with the hematopoietic stem cell. As described by Wilson and Trumpp (2008), stem cells are functionally defined as cells that can both self-renew (maintain their numbers at a constant level) and give rise to all mature cells in the tissue in which they reside. The formation of blood cells is supported by a small population of pluripotent stem cells that exhibit the capacity to self-renew and are capable of extensive proliferation. These cells can also reconstitute all hematopoietic lineages and are capable of long-term reconstitution of the hematopoietic system of recipient animals. The primitive pluripotent stem cells are estimated to comprise 1 in 100,000 bone marrow cells and give rise to multipotent and committed progenitor cells, which represent approximately 2−5 per 1,000 marrow cells (Mihich and Metcalf, 1995). Each of these progenitor cells can generate 100,000 or more maturing progeny. The process of proliferation and differentiation is regulated by more than 25 growth factors, cytokines, and other regulators that may act directly upon one or more of the major lineages of blood cells or interact to influence cell growth (Mihich and Metcalf, 1995). A diagram illustrating the relationships between the major cell types involved in hematopoiesis is shown in Figure 1.

With the exception of lymphocytes where maturation also continues in the thymus, spleen and peripheral tissues, the formation of blood cells in normal human adults occurs almost exclusively in the bone marrow. All mature circulating blood cells have a finite life with the majority of cells being terminally differentiated and unable to replicate (Bagby, 1994). In order

to maintain steady-state levels, the formation of cells in the marrow must equal the rate of cellular senescence and elimination. As a result, the hematopoietic system has a tremendous proliferative capacity with estimates of cell turnover ranging from 130 to 500 billion cells per day in a 70-kg man (Jandl, 1996; Bryderet al., 2006). In addition, the hematopoietic system in the central bone marrow helps respond to a variety of environmental stresses and infection by increasing the blood cell counts of specific lineages when needed (Bagby, 1994; Jaiswal and Weissman, 2009). For example, upon exposure to a hypoxic environment, erythrocyte production will increase without a change in the production of neutrophils. Similar lineage-specific responses are required following exposure to myelotoxic agents. To maintain steady-state blood cell levels and to respond to environmental pressures, hematopoiesis, of necessity, must be a highly regulated process. Historically, the responses to infection and environmental stresses were believed to occur exclusively within the bone marrow. However, as described below, it has recently been shown that an immune response to infection can occur at extramedullary sites due to the homing, proliferation, and differentiation of hematopoietic stem and progenitor cells at these ecotopic sites within the body (Jaiswal and Weissman, 2009; Schulzet al., 2009).

As indicated above, the hematopoietic stem cells normally reside within the bone marrow, a tissue with specialized vasculature and shielding that provides an excellent environment for the development of blood cells (Papayannopoulou and Scadden, 2008). In addition to their ability to self-renew, primitive pluripotent hematopoietic stem cells give rise to a number of multipotent progenitor cells, which, in turn, give rise to oligopotent progenitor cells (see Figure 1 and Bryderet al. [2006]). Among these, the committed lymphoid progenitors give rise to mature B lymphocytes, T lymphocytes, and natural killer (NK) cells whereas the common myeloid progenitors give rise to granulocyte-macrophage progenitors (which differentiate into monocytes/macrophages and granulocytes), and megakaryocyte/erythrocyte progenitors (which differentiate into megakaryocytes/platelets and erythrocytes). Both the myeloid and lymphoid progenitor cells have also been proposed to form dendritic cells, which play a role in regulating the immune system. In addition to these major types of blood cells, a number of the cell types, for example, the granulocytes can further differentiate into more specialized blood cells such as neutrophils, eosinophils, and basophils. As a result, the number of unique cell types derived

from the hematopoietic stem cell is quite large and, as indicated above, the total number of individual cells formed per day numbers in the hundreds of billions.

Hematopoietic stem and progenitor cells are commonly identified based on the presence or absence of lineage markers or antigen expression on the cell surface or in the cytoplasm. As presented by Bryder and associates, the most primitive hematopoietic stem cell identified to date in humans exhibits the cell surface markers, $Lin^{-}CD90^{+}CD38^{-}CD34^{+}$ meaning that it is negative for the lineage differentiation surface antigen Lin, namely $B^{-}G^{-}M^{-}T^{-}$ (B220 for B cells, Gr-1 for granulocytes, Mac-1 for myelomonocytic cells, and CD4 and CD8 for T cells), negative for the surface antigen CD38 and positive for the surface antigens CD90 and CD34 (Bryderet al., 2006; Li and Li, 2006). As described by Iwasaki and Akashi (2007) and (Bryderet al., 2006), the lineage markers and differentiation pathways differ in notable ways between the mouse and the human.

While hematopoietic stem and progenitor cells normally reside in specialized niches in the bone marrow, they can be mobilized into the peripheral blood either at low levels spontaneously or in large numbers as a result of cytokine or chemical treatment (Levesqueet al., 2007; Schulzet al., 2009). These mobilized cells remain in circulation for only short periods of time (minutes to hours) before homing to another peripheral tissue or returning to the bone marrow. As a result, there appears to be a constitutive recirculation of hematopoietic stem and progenitor cells between the bone marrow, extramedullary tissues, and the lymphoid compartments (Schulzet al., 2009). Consequently, it is theoretically possible for DNA damage or other types of potentially leukemogenic alterations to affect hematopoietic stem cells while they circulate in the blood and extramedullary spaces. Upon exposure to mobilizing agents such as specific chemokines, toxicants, antibodies, or growth factors, or under conditions of stress or myelosuppression, large numbers of these stem and progenitor cells can be released into the peripheral blood (Levesqueet al., 2007). Clinically, these mobilized cells can be harvested for use in bone marrow transplantation. The natural role of mobilization is not fully known, but there is evidence that the circulating hematopoietic stem and progenitor cells may help replenish tissue-residing myeloid cells such as specific monocytes, macrophages, and dendritic cells or help in rapidly responding to tissue injury and infection (Jaiswal and Weissman, 2009; Schulzet al., 2009).

3. ORIGINS OF LYMPHOHEMATOPOIETIC NEOPLASIA

As with other cancers, leukemogenesis and lymphomagenesis are multi-step processes involving a series of genetic and epigenetic alterations involved in the transformation of a normal cell into a malignant cell. The various lymphohematopoietic cancers are believed to originate in specific types of pluripotent or lineage-restricted cells at different stages in hematopoiesis (see Figure 2; Greaves, 1999). As illustrated in the figure, leukemias and lymphomas can originate within many types of hematopoietic or hematopoietic-forming cells. With a few rare exceptions, most leukemias and lymphomas originate at the hematopoietic stem cell stage or at later progenitor or lineage-restricted stages. For example, most adult leukemias of myeloid origin (AML, MDS, and CML) as well as adult ALL are believed to originate at the pluripotent stem or progenitor cell stage whereas childhood leukemias are believed to originate during a subsequent stage of differentiation at either the lineage-restricted lymphoid or myeloid stem cell stage. For most types of adult AML, the key leukemic transformations appear to occur in hematopoietic stem cells (Warneret al., 2004). However, for APL, the key transformative event may occur at the committed myeloid progenitor stage (Passegueet al., 2003; Warneret al., 2004). For a few others, such as those possessing the MLL-ENL fusion gene, the transformative event can occur either at the pluripotent or the committed stem cell stage (Cozzioet al., 2003). In contrast, many lymphomas (NHL, Hodgkin lymphoma, Burkitt lymphoma) and all myelomas, as well as, several rare leukemias/lymphomas (adult T-cell leukemia, prolymphocytic leukemia, hairy cell leukemia) and one common (CLL) leukemia are believed to originate in mature lymphoid cells(Greaves, 1999; Harriset al., 2001). An understanding of the origin of these cancers can be useful for grouping various lymphohematopoietic cancers and can provide insight into the cell types targeted by carcinogenic agents.

Consistent with the multi-step nature of leukemogenesis, over 300 different genetic alterations and mutations have been identified (Kelly and Gilliland, 2002). Indeed, a recent examination of alterations affecting the MLL gene, a cancer-related gene located at band 11q23, in pediatric and adult leukemias, identified a total of 87 different rearrangements, primarily translocations, involving this one gene (Meyeret al., 2006). While most of the detected alterations are rare, certain translocations and genes are more prevalent and are typically associated with specific leukemic subtypes (Bhatiaet al., 1999; Greaves and Wiemels, 2003).

Many of these genetic alterations can only be detected at the molecular level. However, others have been detected using cytogenetic, molecular cytogenetic and genomic approaches. Nonrandom chromosomal alterations are detected in the neoplastic cells of a majority of patients with leukemias or lymphomas, and the identification of genes involved in these alterations has provided valuable insights into leukemogenesis and lymphomagenesis in humans (Chen and Sandberg, 2002; Mrozeket al., 2004; Pedersen-Bjergaardet al., 2006; Qianet al., 2009). Because of their importance, an overview of genetic changes in the development of leukemia is described below.

Common clonal cytogenetic changes seen in leukemias include alterations in chromosome number such as loss or gain of one or more chromosomes (e.g., monosomy 7 and trisomy 8, respectively), balanced and unbalanced chromosome translocations, deletions, or inversions involving specific chromosomal regions as well as complex arrangements involving combinations of the above. In some cases, these are a reflection of the genetic instability that is common in many types of cancers. However in many cases, these are highly specific involving genes that are directly involved in the cancer process. For example, the translocation between chromosomes 15 and 17, (t(15;17)(q22;q12-21)) that is characteristic of the promyelocytic form of AML (FAB M3), results in a fusion gene involving the PML gene on chromosome 15 and the retinoic acid receptor *alpha* (RARα) gene on chromosome 17. This hybrid gene blocks differentiation of the developing myeloid cells at the promyelocytic stage (Downing, 1999), a characteristic feature of the disease. As seen in Table 4, significant differences have been seen in the karyotypes of patients who have developed leukemia following therapy and those who have no history of exposure to chemotherapy or other leukemogenic agents. The former are called t-AML and the latter, *de novo* leukemias.

In addition to these microscopically visible chromosomal alterations, mutations at the molecular level affecting specific cancer-related genes such as RAS, FTL3, GATA1, and TP53 have also been seen in t-AML and *de novo* leukemias at varying frequencies (see Table 5). For example, mutations in genes of the receptor tyrosine kinase/RAS-BRAF signal transduction pathway are reported to be present in over 50% of *de novo* AML (Christiansenet al., 2005). These occur through many mechanisms including base pair substitutions, frame shifts, internal tandem duplications, gene fusions, and splicing errors (for examples in AML1, see [Roumieret al., 2003]). In addition, epigenetic alterations such as changes in the methylation patterns in

leukemia-related genes or their promoter regions have also been seen in many types of leukemia, including t-AML (Zhenget al., 2004; Pedersen-Bjergaardet al., 2006; Nerviet al., 2008).

In recent years, researchers have begun to identify patterns among the myriad of translocations, gene arrangements, and point mutations involved in myeloid leukemias and have created a model for leukemogenesis (Deguchi and Gilliland, 2002; Kelly and Gilliland, 2002). According to the model proposed by (Kelly and Gilliland, 2002)

> AML is the consequence of collaboration between at least two broad classes of mutations. Class I mutations, exemplified by constitutively activated tyrosine kinases or their down stream effectors, such as BCR/ABL, TEL/PDGFβR, N-RAS, or K-RAS mutants, or constitutively activated FLT3, confer a proliferative or survival advantage to hematopoietic cells. When expressed alone, these mutant genes confer a CML-like disease characterized by leukocytosis with normal maturation and function of cells. Class II mutations result in loss of function of transcription factors that are important for normal hematopoietic differentiation and include the AML1/ETO, CBFβ/SMMHC, PML/RARα, and NUP98/HOXA9 fusions as well as point mutations in hematopoietic transcription factors such as AML1 and C/EBPα. These mutations would also be predicted to impair subsequent apoptosis in cells that do not undergo terminal differentiation. When expressed alone, these mutations may confer a phenotype like most MDS. Regardless of the timing or order of acquisition of mutations, individuals who accrue both Class I and Class II mutations have a clinical phenotype of AML characterized by a proliferative and/or survival advantage to cells and by impaired hematopoietic differentiation.

A list of the gene mutations seen in patients with t-MDS or t-AML separated into these two mutation classes is shown in Table 6.

More recently, additional interrelationships between new and previously identified genetic alterations, leukemogenic agents, and types of leukemia have been reported (Christiansen et al., 2001, 2004; Haradaet al., 2003; Zhenget al., 2004; Klymenkoet al., 2005; Rege-Cambrinet al., 2005; Wiemelset al., 2005). As illustrated by (Pedersen-Bjergaardet al., 2008), the interactions between these various genes can become quite complicated, and the outcome of these interactions is not fully understood. It should also be noted that some genes such as TP53 do not easily fit within this classification scheme, which suggests that other types of genetic changes are likely to be necessary for the conversion of a normal hematopoietic stem or progenitor cell into a fully transformed leukemic cell (Pedersen-Bjergaardet al., 2008).

4. LEUKEMIA- AND LYMPHOMA-INDUCING AGENTS

While most leukemias occur in individuals with no obvious exposure to radiation or chemical carcinogens (*de novo* leukemias), a significant number, known as secondary leukemias develop in individuals who have previously been exposed to radiation, industrial chemicals, or chemotherapeutic agents. Approximately 40 years ago, the IARC began evaluating chemicals (and later other types of agents) for their ability to induce cancer in humans. Since 1971, IARC has evaluated more than 900 agents (including exposure circumstances) and identified more than 100 as being carcinogenic to humans (classified as Group 1: *Carcinogenic to Humans*[IARC, 2010]). Another 66 have been classified in Group 2A, which indicates agents that are *Probably Carcinogenic to Humans*. Among the 100+ agents in Group 1, approximately 25% have been established as causing a lymphohematopoietic cancer (see Table 7). These include eight therapeutic drugs or mixtures, five industrial chemicals or contaminants, two immunosuppressive drugs, six forms of radiation, two occupational or lifestyle exposures, and six infectious agents. Thus, leukemias and lymphomas represent one of the most common types of cancer induced by a wide variety of carcinogens. In addition, three other Group 1 carcinogens (see Table 7), which induce cancer at other sites, are also thought to be likely to induce either a leukemia or lymphoma. Of the 66 Group 2A agents, there is evidence based either on human studies, animal bioassays, or structural similarities that at least 10 of these chemicals are also likely to cause leukemia in humans. Table 7 lists the Group 1 and 2A agents that have been established, or are likely to cause leukemia or lymphoma, as well some of their characteristics. The same list of agents with key information related to the likely mechanisms responsible for the lymphohematopoietic cancers is shown in Table 8.

In examining the information in Tables 7 and 8, a number of general patterns become apparent. Leukemias are the primary type of cancer induced by the chemical agents, and most of these are ANLLs (synonymous with AML). These were almost always induced by agents that are either directly DNA-reactive or that can be metabolized (or otherwise converted) into DNA-reactive species. Many of the leukemogens are bifunctional alkylating agents; chemicals that form adducts on DNA bases involved in base-pairing such as the 0^6 of guanine or induce chromosomal damage through the inhibition of topoisomerase II. The primary mode of action for these agents is through the induction of mutations, either gene mutations or chromosomal

mutations. Consistent with their proposed mutagenic mode of action, most of the leukemia-inducing agents have been reported to induce structural chromosome aberrations in the peripheral blood of exposed humans. Myelotoxicity is also commonly seen in humans (and animals) exposed to these leukemogenic agents. Exposure to radiation in various forms was frequently associated with ALL and CML, in addition to ANLL. These are also likely due to the effects of ionizing radiation on DNA, either directly or indirectly, and are believed to occur through a mutagenic mode of action.

In contrast to these DNA-damaging agents, exposure to a variety of infectious agents is causally related to the formation of lymphoid neoplasms. The induced lymphomas appear to be primarily associated with chronic infection with either viruses or *Helicobacter* bacteria that are immunomodulating and/or specifically target lymphoid cells. The two chemical agents, cyclosporine and azathioprine, which also induce NHL, are also strongly immunosuppressive. In addition, TCDD, which may induce NHL, is also immunosuppressive, so this could be the mechanism underlying its lymphoma-inducing effects. Although not reviewed by IARC and, hence, not presented in Tables 7 and 8, autoimmune disorders and other diseases associated with immune stimulation and inflammation are increasing recognized from large consortia studies as risk factors for lymphoma (Vajdic et al., 2009, Ekstrom Smedby et al., 2008; Cocco et al., 2008; Nieters et al., 2006).

Similar to the Group 1 agents, the Group 2A leukemogens are associated with the induction of ANLL. For chemicals for which information is available, these agents are also myelotoxic and clastogenic and are believed to most likely induce their leukemogenic effects through a mutagenic mechanism.

In summary, the vast majority of the leukemia-inducing agents are believed to act through a mutagenic mode of action whereas the lymphoma-inducing agents most likely act through immunomodulation and related effects. An overview of the major classes of leukemia-inducing agents is presented below.

5. OVERVIEW OF THE MAJOR CLASSES OF LEUKEMIA-INDUCING AGENTS

5.1. IONIZING RADIATION

As a result of its widespread medical, military, and energy-related uses, large numbers of people have been exposed to ionizing radiation, and its adverse effects have been extensively documented (IARC, 2000b, 2001; UNSCEAR, 2000a, b; Ron, 2003; NRC, 2006). Exposure to ionizing radiation has been shown to result in numerous types of cancer including several types of leukemia as well as adverse effects that are likely to be involved in leukemogenesis including myelotoxicity, immune suppression, and genetic damage leading to chromosomal and gene mutations. The earliest association between radiation and cancer was seen for leukemia, and it has been repeatedly seen in numerous population studies including those exposed through medical, military, and environmental exposures (IARC, 2000b, 2001; UNSCEAR, 2000b; Ron, 2003; NRC, 2006).It should be noted that there are a variety of types of radiation and radioactive materials. Most of the studies that have been conducted have investigated the effects of ionizing radiation, which for simplicity, will be considered as one individual agent in this section. Assessing the risks associated with radiation exposure is challenging and is influenced by the type of radiation, the tissue dose, the proportion of the body exposed, the extent of cell killing, and the DNA-repair capacity of the individual or tissue (Curtiset al., 1994). Host factors such as age, sex, genetic composition, and health of the exposed individuals can also influence the risk of radiation-induced leukemia.

All age groups are affected, but children, in particular, have been shown to be at an elevated risk for radiation-induced leukemia as seen in the Life Span Study of the atomic bomb survivors in Hiroshima and Nagasaki. Among the survivors who were exposed to both *gamma*, and to a lesser extent, neutron radiation, the highest leukemia risks were seen in children (Prestonet al., 1994, 2004). Significant dose-related increases were seen for ALL, AML, and CML, with the excess risks for ALL and CML being approximately 100% higher in the exposed males than in the females. When the leukemias were reclassified using the FAB classification scheme, all AML subtypes were present with a predominance of myeloblastic leukemias with and without maturation (M1 and M2) (Matsuoet al., 1988). Among the ALL cases, most cases exhibited the L2 subtype, but a significant portion also showed the L1 subtype. Latency periods were shorter for those under 15 years of age with a leukemia peak at 5–7 years post exposure as

compared to later peaks for those exposed at later ages (Kamada and Tanaka, 1983). The leukemia risk also decreased more rapidly in children as compared to those in older age groups. Overall, the risks to children were highest during the period from 1950 to 1965 and returned to near background levels thereafter (Prestonet al., 1994).

Similarly, the use of radiation for medical purposes has been associated with increases in leukemia. Increased risk of leukemia has been reported following the use of radiation for diagnostic tests, for the treatment of benign diseases, and following radiotherapy for cancer (Ron, 1998, 2003). For hematopoietic and lymphoid tissues that are diffuse, a significant portion of the tissue must be irradiated to increase the incidence of neoplasia (Storeret al., 1982). The leukemia risks from medical irradiation appear to have diminished in recent years due to a use of lower and more restricted doses as well as changes in therapeutic strategy in which high doses are applied within limited fields. High radiation doses (above 3−4 Gray) result in extensive killing of marrow-containing progenitor cells and have been associated with a reduced risk of developing leukemia (Boiceet al., 1987; NRC, 1990; Curtiset al., 1994).

5.2. CHEMOTHERAPEUTIC AGENTS

Following the initiation of intensive chemotherapy with genotoxic agents, increases in therapy-related leukemias began to appear (Seiber and Adamson, 1975; Kantarjian and Keating, 1987; Levine and Bloomfield, 1992; Leoneet al., 1999). These leukemias, also known as treatment-related or secondary leukemias, consisted primarily of AML, although a small increase in therapy-related ALL has also been seen (Hungeret al., 1992; Andersenet al., 2001). With increased periods of follow-up, increases in other types of solid tumors have also been observed (Tuckeret al., 1988; Loescheret al., 1989; Boffetta and Kaldor, 1994; van Leeuwenet al., 1994; Vega-Stromberg, 2003; Traviset al., 2005; Hodgsonet al., 2007).

Over time as new agents and therapeutic strategies have been employed, additional agents have been recognized as inducing leukemia in humans. Indeed as seen in Table 7, chemotherapeutic drugs comprise the largest group of agents generally recognized as human leukemia-inducing agents. Currently, therapy-related leukemias constitute 10 to 20% of the leukemia cases seen at major medical institutions (Deschler and Lubbert, 2006; Pedersen-Bjergaardet al., 2007).

The identification of specific agents involved in leukemogenesis and the interpretation of many of the studies can be challenging due to the use of multiple therapeutic agents, varying dosing regimens, concurrent use of radiotherapy, and variable periods of patient follow-up. Over time, two main classes of leukemogenic therapeutic drugs have been identified—alkylating agents and topoisomerase II inhibitors (Pedersen-Bjergaard and Philip, 1991; Pedersen-Bjergaard and Rowley, 1994; Pedersen-Bjergaardet al., 2006). An overview of the leukemias (including myelodysplastic syndromes) induced by these two classes of chemotherapeutic drugs will be briefly discussed in the following sections.

5.2.1. Alkylating Agent-Related Leukemias

A large number of studies have demonstrated that patients treated with alkylating agent-based chemotherapy are at an increased risk of MDS and AML (Levine and Bloomfield, 1992; Pedersen-Bjergaard and Rowley, 1994; Smithet al., 1994). These risks have been seen for both children and adults and are strongly related to the cumulative dose of the alkylating agent (Pedersen-Bjergaard and Philip, 1987; Tuckeret al., 1987; Hungeret al., 1992; Pedersen-Bjergaardet al., 2000; Pyattet al., 2005). The administered agents also exhibit varying degrees of hematopoietic toxicity, immunotoxicity, and genotoxicity, which can also be affected by the agent, dose, and route of administration (Gale, 1988; Ferguson and Pearson, 1996; Sanderson and Shield, 1996). The incidence of treatment-related MDS and AML (t-MDS/t-AML) in adults treated with antineoplastic drugs has been reported to range from 1% to >20% (Felix, 1998; Leoneet al., 2001). The increases in this type of therapy-related leukemia generally appear 1 to 2 years after treatment and may remain elevated for 8 or more years following the completion of chemotherapy (Pedersen-Bjergaard and Philip, 1987; Pedersen-Bjergaard and Philip, 1991; Davies, 2000; Schonfeldet al., 2006).

In adults, leukemias induced by alkylating agents exhibit characteristics that generally allow them to be distinguished from *de novo* leukemias and those induced by topoisomerase II inhibitors (Pedersen-Bjergaard and Rowley, 1994; Eastmondet al., 2005). These leukemias are typically myeloblastic with or without maturation (FAB M1 and M2 subtypes) and are characterized by trilineage dysplasia and clonal unbalanced chromosome aberrations, most commonly involving loss of the entire chromosome or part of the long arms of chromosomes 5 and 7 (−7, 7q−, −5, 5q−). These t-AML have a modal latency of 4−7 years, and the onset of

the actual leukemia is often preceded by myelodysplasia. It should be noted that AML induced by ionizing radiation tends to exhibit similar features (MDS, clonal unbalanced chromosomal aberrations, etc.) although the range of the FAB subtypes induced by radiation tends to be broader (Matsuoet al., 1988; Philip and Pedersen-Bjergaard, 1988; Gundestrupet al., 2000).

Using structure-activity relationships as well as other predictive approaches with in vivo rodent and *Drosophila* data, Vogelet al. (1998) were able to identify three major categories of DNA-reactive chemical and therapeutic agents. As described by the authors, Category 1 consisted of mono-functional alkylating agents such as ethylene oxide and methyl methane sulfonate, which primarily react at the N7 and N3 moieties of purines in DNA. Efficient DNA repair was the major protective mechanism against the relatively weak genotoxic effects of these agents, which might not be detectable in repair-competent cells. High doses were generally needed for the induction of tumors in rodents. A strong target site specificity for the adverse effects was seen, and this appeared to be related to DNA repair capacity. Category 2 agents such as procarbazine and *N*-nitroso-*N*-ethylurea (ENU) induce both *O*-alkyl adducts and *N*-alkyl adducts in DNA. In general, the induced *O*-alkyl adducts appeared to be slowly repaired, or not repaired, which made these agents potent carcinogens and germ cell mutagens. The inefficient repair of the *O*-alkyl-pyrimidines, in particular, was responsible for their potent mutagenic activity. Category 3 agents such as melphalan and busulfan induced structural aberrations through their ability to cross-link DNA, and this was the major factor contributing to their high genotoxic potency, which appeared to be related to the number of DNA crosslinks per target dose unit that were induced. The genotoxic effects for the Category 3 agents occurred at, or near, toxic levels. For all three categories of genotoxic agents, strong correlations were observed between their carcinogenic potency, acute toxicity, and germ-cell specificity.

5.2.2. Topoisomerase II Inhibitor-Related Leukemias

In the late 1980s, a new type of therapy-related leukemia was recognized that exhibited unusual features that differed from those previously seen following treatment with alkylating agents and radiation (Puiet al., 1989; Pui and Relling, 2000). The affected patients had been treated with etoposide or teniposide, two of a newly developed epipodophyllotoxin class of chemotherapeutic agents (Pedersen-Bjergaard and Philip, 1991). In the ensuing years, these epipodophyllotoxins have become widely used, especially for treating childhood cancers, and a

large number of studies have been published establishing an association between treatment with these drugs and the subsequent development of leukemia (Hauptet al., 1993; Smithet al., 1994; Pedersen-Bjergaardet al., 1995; Pui and Relling, 2000; Leoneet al., 2001; Hijiyaet al., 2009).

The leukemia risk following epipodophyllotoxin therapy was reported to be very high in early studies, with cumulative incidences approaching 19% in some treatment groups (Puiet al., 1989). Interestingly, in some cases, the risk of a secondary cancer appeared to be more closely related to the treatment regimen than to total dose (Puiet al., 1991; Pui and Relling, 2000). Patients receiving epipodophyllotoxins on a weekly or twice-weekly basis had much higher cumulative risks (12.4%) than those receiving the drugs on a biweekly schedule (1.6%). Similar results have been seen in more recent studies (Smithet al., 1999) although others have seen a correlation between cumulative dose and epipodophyllotoxin-induced t-AML (Negliaet al., 2001; Le Deleyet al., 2003). With implementation of newer treatment protocols, the risk of t-AML has been reduced substantially and is now within the range of that seen with alkylating chemotherapeutic agents (Smithet al., 1993; Pui and Relling, 2000). There is also evidence that the combined treatment of topoisomerase II inhibitors with alkylating agents (or cisplatin) confers a greater risk of t-AML than seen with either type of chemotherapeutic agent alone (Sandovalet al., 1993; Smithet al., 1994; Blatt, 1995). In most reported cases, the incidence of t-AML induced by these drugs is estimated to range from 2 to 12% (Felix, 1998; Leoneet al., 2001).

The epipodophyllotoxins exhibit moderate myelosuppression, identifiable chromosomal damage, and their leukemogenic effects by inhibiting topoisomerase II through a process that involves stabilization of the DNA-enzyme complex (Smithet al., 1994; Ferguson and Pearson, 1996). Topoisomerase II is a nuclear enzyme involved in a wide variety of cellular functions, including DNA replication, transcription, and chromosome segregation (Anderson and Berger, 1994; Nitiss, 2009). Leukemias induced following treatment with epipodophyllotoxin-type topoisomerase inhibitors appear from 10 months to 8 years following the initiation of chemotherapy, with a median latency of 2 to 3 years (Smithet al., 1994; Leoneet al., 2001). The induced AMLs are primarily of the monocytic or myelomonocytic subtypes (M4 and M5) and are rarely preceded by a myelodysplastic phase, a pattern that differs significantly from alkylating agent or radiation-induced leukemias (Pedersen-Bjergaard and Rowley, 1994; Smithet al., 1994; Leoneet al., 2001; Pedersen-Bjergaardet al., 2006).

Infrequently, ALL has been reported in patients following treatment with both alkylating agents and topoisomerase II-inhibiting drugs (Hungeret al., 1992; Andersenet al., 2001; Hijiya et al., 2009). Although t-ALLs occur infrequently, they seem to be more common in children under the age of 15 who have previously been treated with a topoisomerase II inhibitor (Andersenet al., 2001).

One of the unique features of t-AML, and to a lesser extent t-ALL, induced by the epipodophyllotoxin-type of topoisomerase II inhibitors, is the presence of clonal-balanced translocations involving the MLL gene (also known as ALL-1, HRX, and HTRX-1) located on the long arm of chromosome 11 (11q23) in the leukemic cells. Cytogenetic studies of patients with leukemias induced by these agents have shown that in over 50% of the cases, the leukemic clone involved a balanced translocation affecting the 11q23 region and another chromosomal partner, usually t(6;11), t(9;11), and t(11;19) (Pedersen-Bjergaard and Rowley, 1994; Smithet al., 1994; Canaaniet al., 1995). In children previously treated with topoisomerase inhibitors, up to 90% of the secondary leukemias have an 11q23 alteration (Canaaniet al., 1995). As indicated previously, to date, 87 rearrangements involving the MLL gene have been identified, and 51 of the translocation partner genes have been characterized at the molecular level (Meyeret al., 2006). The four most common MLL translocation partner genes (AF4, AF9, ENL, and AF10) encode nuclear proteins that are part of a protein network involved in histone H3K79 methylation (Meyeret al., 2006) indicating an important role for this pathway in epipodophyllotoxin leukemogenesis.

Numerous lines of evidence indicate that topoisomerase II as well as DNA-repair enzymes such as those involved in non-homologous end joining play an important role in the formation of the 11q23 translocations. These have been summarized in series of reviews (Greaves and Wiemels, 2003; Aplan, 2006; Felixet al., 2006; Zhang and Rowley, 2006). The presence of topoisomerase II recognition sites has been found in proximity to the translocation breakpoints as have recombinase recognition sites, Alu sequences, DNase hypersensitive sites, and scaffold attachment regions and suggest that multiple types of damage and repair probably contribute to the generation of the observed translocations (Pui and Relling, 2000; Felixet al., 2006; Zhang and Rowley, 2006). Interestingly, in a recent report, Le et al., (2009) reported that the translocation breakpoints within the MLL gene occurred in a highly specific fashion at the base of a secondary DNA structure formed from a palindrome. A stringent topoisomerase II

consensus binding site was located at the apex of the secondary DNA structure. The authors proposed a model in which topoisomerase II facilitates the formation of a secondary structure that results in site-specific DNA strand breakage that is efficiently processed into translocations (Leet al., 2009). This processing most likely occurs through a mechanism involving nonhomologous end joining (Greaves and Wiemels, 2003; Zhang and Rowley, 2006). It should also be noted that the MLL gene has been shown to be prone to breakage during apoptosis, and it has been proposed that the observed translocations occur in hematopoietic cells rescued at an early, reversible stage during the apoptotic process (Stanullaet al., 1997; Bettiet al., 2005; Vaughanet al., 2005; Baseckeet al., 2006). A role for apoptosis has also been proposed in the formation of other leukemia-related translocations (Eguchi-Ishimaeet al., 2001).

5.2.3. Other Likely Leukemia-Inducing Therapeutic Agents

In recent years, evidence has accumulated that other inhibitors of topoisomerase II, such as the anthracycline, anthracenedione, and bisdioxopiperazine derivatives, can also induce secondary leukemias (Xueet al., 1992; Zhanget al., 1993; Blatt, 1995; Andersenet al., 1998; Le Deleyet al., 2003; Mistryet al., 2005; Mayset al., 2010). The leukemias induced by these agents are similar to the epipodophyllotoxins in that they have short latency periods and are infrequently preceded by myelodysplasia. However, they typically exhibit different types of clonal-balanced rearrangements (e.g., t(8;21), t(15;17), and inv(16)) and different FAB subtypes (M2 and M3).

Although azathioprine, 6-thioguanine, and 6-mercaptopurine are primarily associated with immunosuppression and the induction of NHL, a number of studies have suggested that patients treated with these 6-thioguanosine monophosphate-producing drugs are at an increased risk of developing ANLL (Boet al., 1999; Karran, 2006; Yensonet al., 2008). It has been suggested that the risks are higher in patients with low thiopurine *S*-methyltransferase activity and may involve aberrant mismatch repair and microsatellite instability (Boet al., 1999; Karran, 2006). Interestingly, the leukemias of many of these patients also show loss of chromosome 7 or part of chromosomes 5 or 7 (5q− or 7q−) (Yensonet al., 2008).

A summary of the types of leukemia and related lymphoid neoplasms as well as key characteristics of the leukemias induced by different types of leukemia-inducing agents is presented in Table 9. Information on leukemias induced by the bisdioxopiperazine class of

topoisomerase II inhibitors has also been added to facilitate comparisons with benzene. There is recent evidence to suggest that one mechanism by which benzene induces leukemia is through inhibition of topoisomerase II by a mechanism that may be similar to that of the bisdioxopiperazine class of topoisomerase II inhibitors (Mondrala and Eastmond, 2009).

6. MECHANISMS INVOLVED IN t-AML

For more than 20 years, Pedersen-Bjergaard and colleagues have collected information on patients with t-AML and t-MDS who have been treated at their clinic in Copenhagen, Denmark. Based on the genetic alterations seen in this cohort of 140 patients as well as information in the literature, they have identified eight separate pathways that appear to lead either directly to t-AML or lead to t-MDS and then to t-AML. These pathways are illustrated in Figure 3 (from [Pedersen-Bjergaardet al., 2006]). The pathways have been classified into three groups largely based upon the therapeutic agent that was likely responsible for the leukemia. Each of the pathways is described below based on descriptions extracted from their 2006 article (i.e., Pedersen-Bjergaardet al., 2006).

Pathway I in the figure was characterized by patients who developed t-MDS prior to t-AML and exhibited either loss of chromosome 7 or part of the long arm of that chromosome (7q−). These patients also did not exhibit the recurrent balanced translocations that are associated with AML. Most of these patients (35/39) had been treated with alkylating agents, and most (35/39) presented with t-MDS prior to t-AML. Methylation of the p15 promoter, considered a late event in leukemogenesis, was seen in 84% of the patients. In addition to the chromosome 7 changes, the leukemias of a significant portion (15/39 or 38%) of these patients had point mutations in the AML1 (also known as RUNX1) gene. A number of these patients also had mutations in either the TP53 tumor suppressor gene or an activating mutation in the RAS oncogene.

Pathway II predominated in patients that exhibited loss of all (−5) or part of the long arm of chromosome 5 (5q−). Approximately half of the patients in this group also had −7 or 7q− alterations. As with Pathway I, onset of this disease is closely related to the use of alkylating agent chemotherapy (27/34) and an initial presentation as t-MDS (26/34). Seventy-seven percent of these patients exhibited mutations in TP53. The patients also often present with a complex karyotype, loss of part of the short arm of chromosome 17 (17p−), or showed an amplification or duplication of chromosome bands 11q23 or 21q22. Methylation of the p15 promoter occurred in 80−90% of the patients of this group.

Pathway III was characterized by balanced translocations involving the 11q23 chromosome band and one of many partner chromosomes. These translocations frequently

occurred in patients who had been previously treated with topoisomerase II inhibitors and exhibited AML of the FAB subtypes M4 or M5. Three of the 11 patients in this group had a RAS mutation, and another 3 had a BRAF mutation. Methylation of the p15 promoter was seen in 50% of the patients.

Pathway IV occurred in patients with balanced translocations involving chromosome bands 21q22 or 16q22 leading to chimeric rearrangements involving the core binding factor genes AML1 or CBFB. These chromosomal changes are generally associated with previous treatment with topoisomerase II inhibitors, most commonly of the anthracycline class. While patients in this group with a t(3;21)(q26;q22) often present as t-MDS, most of the others present directly with t-AML. Chromosome 7 alterations were also seen in five of nine patients with 21q22 translocations. Point mutations in c-Kit and PTPN11 were seen in a few patients. Methylation of the p15 promoter was seen in 83% of the patients.

Pathway V occurred in only two patients and is characterized by a translocation between chromosomes 15 and 17 involving the PML and RARA genes. Therapy-related promyelocytic leukemia (M3) that exhibits the characteristic t(15;17) has been reported to occur in patients treated with doxorubicin or mitoxanthrone. One of the patients in this group also had a mutation due to FLT3 internal tandem duplication.

Pathway VI is an uncommon pathway in which t-AML patients exhibit balanced translocations involving the NU98 gene at chromosome band 11p15. None of the 140 patients in the Copenhagen series exhibited this pattern.

Pathway VII exhibits a normal karyotype, and most often presents directly as t-AML. Approximately 17% of the patients in the Copenhagen series fell within this group and have not been consistently associated with any previous type of chemotherapy. The mutations seen are also commonly seen in *de novo* leukemias suggesting that these may represent sporadic cases of *de novo* leukemia occurring in these patients. Methylation of the p15 promoter was only seen in 50% of these patients.

Pathway VIII is composed of patients that exhibit unique or unusual chromosome alterations and represents 14% of the Copenhagen cohort. These cases do not show an association to any specific type of previous therapy and may also represent cases of *de novo* leukemia. Methylation of the p15 promoter was also uncommon occurring in 40% of the cases.

Consistent with the description presented above, patients with t-AML with leukemic cells exhibiting loss of all or part of chromosomes 5 or 7, frequently present initially with t-MDS and have often been previously treated with alkylating agent chemotherapeutic drugs. In contrast, t-AML exhibiting certain specific reciprocal translocations such as t(11q23) and t(21q22) occur in patients that were previously treated with a topoisomerase II-containing chemotherapeutic regimen and develop without a preceding MDS.

7. FACTORS CONFERRING AN INCREASED RISK OF INDUCED LEUKEMIA

7.1. MYELOSUPPRESSION AND IMMUNOTOXICITY

Myelosuppression and immunotoxicity frequently accompany exposure to leukemia-inducing agents, particularly those such as the chemotherapeutic drugs, ionizing radiation, and benzene, for which leukemogenicity has been clearly established (Ferguson and Pearson, 1996; Eastmond, 1997). The number of individuals affected and the magnitude of toxicity are influenced by the agent and dose-related factors such as total dose, dose per treatment, schedule, and route of administration as well as individual host factors (genetic susceptibility, prior therapy, health status, etc.) (Gale, 1988). A brief overview of the myelosuppressive effects of cancer therapeutic drugs has been written by Gale (1988) and is the basis for the following description. The severity of myelotoxicity induced by antineoplastic drugs varies considerably by chemical class. For drugs associated with t-AML, moderate-to-severe effects are generally seen. The epipodophyllotoxins, cisplatin, and procarbazine typically produce more moderate toxicity whereas severe effects are more common for the alkylating agents, the anthracyclines, and the nitrosoureas.

The period between dosing and the onset or appearance of the myelosuppression is also related to the class of agent. For some agents such as ionizing radiation, the onset of myelotoxicity occurs within 0 to 48 hours after exposure. For others, longer periods are required. The onset of myelosuppression by the alkylating agents and anthracyclines occurs 1 to 3 weeks following exposure and is believed to be due to the effect of these agents on immature hematopoietic cells that becomes more evident as the more mature blood cells die and require replacement. Myelosuppression induced by the nitrosoureas and mitomycin C is less frequent and occurs 4 to 8 weeks after treatment. This delayed effect is believed to be due to a relatively selective effect on immature stem cells. However, the onset of this delayed effect is dose-dependent. A two- to three-fold increase in dose reduces the onset of myelotoxicity to 1 week. For some drugs such as busulfan, the manifestation of the myelotoxic effects is considered to be latent and may only be manifested under stress-related conditions.

In most cases, the induced myelotoxicity is transient with the blood cell counts returning to normal following the cessation of treatment or exposure (Hendry and Feng-Tong, 1995; Ironset al., 2005). However, in some cases, the induced myelosuppression can be more

persistent and progress to pancytopenia or infrequently to aplastic anemia, a condition that confers a much greater risk of developing leukemia (~10%) (Aksoyet al., 1984; Jandl, 1987; Oharaet al., 1997; Imashukuet al., 2003). Increased risks have also been seen for those who have previously exhibited less severe forms of bone marrow toxicity. Studies of benzene-exposed workers have shown that the leukemia mortality rate was much higher for workers who had previously been diagnosed with bone marrow poisoning (700 per 10^6 person-years) as compared to those exposed to, but not poisoned by, benzene (14 per 10^6 person-years), and particularly as compared to the general population (2 per 10^6 person-years) (Yin and Li, 1994). In one report, 36% of the benzene leukemia cases had a history of benzene poisoning with leukopenia or pancytopenia (Yinet al., 1994). However, this also indicates that for most cases, clinically detectable myelotoxicity may not be observed. It should also be noted that at lower exposure levels, the decreases in cell counts occurring in exposed groups may fall within what is considered the normal clinical range (Quet al., 2002; Lanet al., 2004). This highlights one of the challenges in using myelotoxicity as a biomarker, as the normal range varies considerably in adults. For example, the mean white blood cell count in adults is $7{,}200 \times 10^3/\mu L$ with a 95% range from 3,900 to $10{,}900 \times 10^3/\mu L$ (Jandl, 1996).

7.2. GENETIC POLYMORPHISMS

Inherited polymorphisms in genes involved in xenobiotic metabolism and other cellular processes have been associated with increased risks of myelotoxicity or leukemia in numerous studies of patients or workers exposed to leukemogenic agents. In some instances, similar associations have been seen in follow-up studies by other investigators. However, in a significant number of cases, the results have either not been repeated or have not been reproducible. Consequently, it is difficult to make firm conclusions about many of the reported polymorphisms. Several recent reviews on polymorphisms and leukemia have been published that the reader may want to refer to for further details (Cheok and Evans, 2006; Cheoket al., 2006; Sinnettet al., 2006; Seedhouse and Russell, 2007). The following is a brief overview of some of the genetic polymorphisms involved in DNA metabolism, repair, and xenobiotic metabolism that have been repeatedly associated with altered risks of developing leukemia, particularly induced leukemias.

Since most leukemogens are genotoxic and exert their effects by damaging DNA, the DNA repair capacity of the bone marrow is likely to have a significant influence on the risk of t-AML. Indeed, individuals with congenital deficiencies in enzymes that are involved in DNA repair such as ataxia telangiectasia, Bloom syndrome, and Fanconi anemia are at significantly higher risk for developing leukemia and other lymphohematopoietic cancers (Segel and Lichtman, 2004). Individuals with these and other uncommon genetic syndromes such as neurofibromatosis 1 are also at an increased risk of t-AML following treatment with radiation, alkylating agents, and/or topoisomerase II inhibitors (Mariset al., 1997; Seedhouse and Russell, 2007).

Genetic polymorphisms in DNA repair genes that occur more frequently in the population can also confer an increased risk of t-AML. Defective mismatch repair is often manifested by microsatellite instability in the cancer cells. Microsatellite instability is frequently seen in leukemias, particularly in t-AML, where it has been reported to occur in ~50% of the cases (Karranet al., 2003; Seedhouse and Russell, 2007). In contrast, less than 5% of *de novo* leukemias exhibit microsatellite instability. While the basis for this instability is still unknown, factors that may contribute are deficiencies in DNA-mismatch repair enzymes. In a fairly recent report, the hMSH2 mismatch repair variant was shown to be significantly overrepresented in t-AML patients that had previously been treated with 0^6-guanine-forming alkylating agents including cyclophosphamide and procarbazine, as compared with controls (Worrillowet al., 2003). Similarly, polymorphisms in genes involved in DNA repair (e.g., WRN, TP53, hOGG1, XRCC1, ERCC3, and BRCA2) have been reported by a number of investigators to be associated with a decrease in white blood cell counts or an increase in chromosomal damage in benzene-exposed workers or workers previously poisoned by benzene (Shenet al., 2006; Kimet al., 2008; Wuet al., 2008; Hosgoodet al., 2009; Sunet al., 2009).

Polymorphisms affecting DNA metabolism have also been reported to confer an increased risk of t-AML. Thiopurine methyltransferase (TMPT) catalyzes the *S*-methylation of thiopurine medications such as 6-mercaptopurine and 6-thioguanine, which are commonly used as chemotherapeutic agents. As summarized from Cheok and Evans (2006), the thiopurine methyltransferase pathway is the primary mechanism for inactivation of thiopurines in hematopoietic tissues. The link between thiopurine methyltransferase polymorphisms and mercaptopurine toxicity has been extensively investigated, and studies have shown a strong

relationship between thiopurine methyltransferase deficiency polymorphisms and hematopoietic toxicity. Three variant alleles are responsible for >95% of the cases with low or intermediate thiopurine methyltransferase activity. Patients homozygous or heterozygous for the low activity alleles are inefficient at detoxifying the mercaptopurines and accumulate high concentrations in their hematopoietic tissues. If their administered doses are not modified, they are at high risk for severe hematopoietic toxicity. Inherited thiopurine methyltransferase deficiency has also been associated with a higher risk of t-AML, particularly in ALL patients treated with topoisomerase II inhibitors (Thomsenet al., 1999; Gadneret al., 2006). It has been postulated that the increased risk may be due to an interference of 6-thioguanine or methylated 6-mercaptopurine with DNA repair after DNA damage has been induced by other chemotherapeutic agents.

The influence of polymorphisms in other xenobiotic metabolizing genes on the incidence of leukemia has been the subject of many investigations (Cheoket al., 2006; Leoneet al., 2007; Seedhouse and Russell, 2007; Guillem and Tormo, 2008; Leoneet al., 2010). In many cases, there was no difference between the frequencies seen in t-AML patients as compared to *de novo* leukemia patients or a control cohort. A number of studies have indicated that individuals with genes coding for nonfunctional or less active copies of various glutathione-*S*-transferases, CYP3A4, and NADPH-quinone-oxidoreductase 1 (NQO1) have an increased risk for developing t-AML following chemotherapy. However, these results have not consistently been seen. The relationship between NQO1 and leukemia is presented below as an example.

Polymorphisms in NQO1, an enzyme involved with the reduction of quinones and protection against oxidative stress, have been repeatedly associated with the development of leukemia. Studies have reported that an inactivating polymorphism in NQO1 (the C609T slow variant) was overrepresented in patients with t-AML (Larsonet al., 1999), in those with *de novo* AML (particularly those with translocations or an inv (16) clonal aberration [Smithet al., 2001]), and in infant leukemias with a 11q23 karyotype, and infants and children with the t(4;11) form of ALL (Wiemelset al., 1999; Smithet al., 2002). While these initial studies indicated a consistent association with a number of different leukemia types, more recent studies have been less consistent with many not showing an association (Blancoet al., 2002; Sirmaet al., 2004; Eguchi-Ishimaeet al., 2005; Maliket al., 2006).

Genetic polymorphisms affecting NQO1 have also been associated with increased myelotoxicity and may confer an increased risk of leukemia. For example, benzene-exposed

individuals who were rapid CYP2E1 metabolizers and had the C609T slow variant for NQO1 had a 7.6-fold increased risk of benzene poisoning as compared to exposed individuals with the slow metabolizer phenotype who had one or two of the wild type NQO1 alleles (Rothmanet al., 1997). In another study by this research group, different NQO1 polymorphisms, as well as a polymorphism in myeloperoxidase, an enzyme implicated in the bioactivation of benzene's quinone metabolites in the bone marrow, were associated with lower blood cell counts in benzene-exposed workers (Lanet al., 2004). A similar association between NQO1 and chromosomal damage in the peripheral blood lymphocytes of benzene-exposed was also recently reported by another research group (Kimet al., 2008).

8. EXAMPLES OF SPECIFIC LEUKEMIA-INDUCING CHEMICALS

The information on the mechanisms of action of the various leukemia-inducing agents presented in the following section has been extracted and summarized from the respective IARC monographs.

8.1. MELPHALAN

A modified version of the section below will be published in a forthcoming issue of the IARC monographs.

The antineoplastic drug melphalan is a direct-acting, bifunctional alkylating agent that binds to cellular macromolecules including DNA, RNA, and proteins (Osborneet al., 1995). As a phenylalanine derivative of nitrogen mustard, it is capable of producing a variety of DNA adducts including monoadducts at the N7 of guanine and the N3 of adenine as well as interstrand crosslinks - premutagenic lesions that are believed to play a critical role in its toxic and carcinogenic effects (Povirk and Shuker, 1994; Lawley and Phillips, 1996; GlaxoSmithKline, 2007). In the classification scheme of Vogel et al., 1998, melphalan is a Category 3 agent that would be expected to be a potent mutagen and carcinogen.

Melphalan has been tested for genotoxicity in an assortment of short-term tests, with positive results seen in a wide variety of assays both in vitro and in vivo(IARC, 1987a, b). Increased frequencies of chromosomal aberrations and sister chromatid exchanges (SCEs) occurring in the peripheral blood lymphocytes have also been reported in multiple studies of patients treated therapeutically with melphalan (IARC, 1987a; Raposa and Varkonyi, 1987; Mamuriset al., 1989, 1990; Poppet al., 1992; Amielet al., 2004). Patients treated with this anticancer agent have also exhibited hematotoxicity and immunosuppression (Goldfranket al., 2002; GlaxoSmithKline, 2007).

As indicated in the most recent IARC evaluation, patients treated with melphalan are at a significantly elevated risk of developing ANLL (Grosseet al., 2009) (see Table 7). Leukemias that have developed in patients previously treated with melphalan (often in combination with other agents) have shown the alterations involving chromosomes 5 and 7 that, as described above, are characteristic of t-AML induced by alkylating agents (Rodjeret al., 1990). While there is some evidence that melphalan may directly induce damage targeting chromosomes 5 or 7

(cf. Mamuriset al. [1989, 1990] and Amielet al. [2004]), this drug has also been reported to induce nonspecific chromosomal alterations in a variety of experimental models and in the lymphocytes of treated patients as indicated earlier. The detection of elevated levels of chromosome aberrations in the peripheral blood lymphocytes of the treated patients is of particular note, as multiple prospective studies have now shown that individuals with increased levels of chromosome aberrations or micronuclei in these cells are at increased risk of developing cancer later in life (Hagmaret al., 1998; Liouet al., 1999; Smerhovskyet al., 2001; Hagmaret al., 2004; Boffettaet al., 2007).

8.2. ETHYLENE OXIDE (largely summarized from IARC, 2008b)

Ethylene oxide is a direct-acting alkylating agent that has been shown to bind to DNA, RNA, and protein. The major DNA adduct recovered in vivo is *N7*- (hydroxyethyl) guanine, an adduct that in not considered to be particularly mutagenic. Additional adducts such as 3-(2-hydroxyethyl)-adenine and O^6-(2-hydroxyethyl)guanine, which would be expected to be more mutagenic, are either not detected or are detected at very low levels (Walker et al., 1992). Ethylene oxide is readily metabolized to non-DNA reactive products by glutathione-*S*-transferases and epoxide hydrolases, and this is likely to reduce the concentrations of ethylene oxide that are able to reach the DNA. In the classification scheme of Vogelet al., 1998, ethylene oxide is a Category 1 agent that would be expected to be a relatively weak mutagen and carcinogen in vivo as compared to other, primarily antineoplastic, alkylating agents.

Ethylene oxide has been shown to be genotoxic and mutagenic in numerous assays in both somatic and germ cells, and in both prokaryotic and eukaryotic organisms (IARC, 1994, 2008b). It is highly active in *in vitro* systems, with lesser activity being seen in vivo. Numerous studies have shown that ethylene oxide can induce point mutations in both reporter genes and cancer genes of multiple tissues in mice and rats. Based on these studies, however, ethylene oxide was considered to be a relatively weak point mutagen *in vivo*. Ethylene oxide was shown to induce chromosomal damage in rodents, but observable damage occurred only at high concentrations indicating that it is also a relatively weak clastogen in experimental animals. Somewhat surprisingly, increased frequencies of chromosomal aberrations have been seen in the peripheral blood lymphocytes of ethylene oxide-exposed workers in 18 of 24 studies that were evaluated (IARC, 2008b). As indicated above, individuals with elevated frequencies of

chromosomal aberrations in their peripheral blood are at an elevated risk of developing cancer. Ethylene oxide induced lymphohematopoietic cancers in female mice (lymphomas) and male and female rats (mononuclear cell leukemia) in chronic bioassays. In contrast to most other leukemia-inducing agents, exposure to ethylene oxide has not been associated with myelotoxicity in humans.

In two fairly recent studies, an elevated frequency of mutations or a change in mutational spectra was seen in the tumors of ethylene oxide-treated mice (Houleet al., 2006; Honget al., 2007). High frequencies of K-*Ras* mutations were detected in the lung, Harderian gland, and uterine tumors of the ethylene oxide-treated animals. A minor increase in mutation frequency and a major change in the mutational spectrum of *Tp53* mutations were also seen in mammary gland tumors of ethylene-oxide treated mice (Houleet al., 2006). The high frequencies of mutations present in these genes, particularly mutations in the critical codons of K-*Ras* and inactivation of *Tp53*, indicate that mutations are induced in the tumors of ethylene oxide-treated mice, and that the changes likely play an important role in ethylene oxide-induced tumorigenesis in these tissues.

There is little known about the mechanisms underlying ethylene oxide-induced tumors in humans. However, activating mutations in the *RAS* family of oncogenes and inactivation of *TP53* have been shown to play critical roles in the development of both spontaneous and chemically induced cancers (Pedersen-Bjergaardet al., 2006; Zarbl, 2006). Of note, activating mutations in *RAS* genes have been shown to occur in up to 30% of AML cases (Byrne and Marshall, 1998). In most cases, it is N-*RAS* that is activated although activation of K-*RAS* is occasionally seen (Byrne and Marshall, 1998; Bowenet al., 2005). The mutations typically occur in codons 12, 13, and 61, sites that are critical for the normal regulation of *RAS* activity. The activating mutations lead to the generation of constitutively activated *RAS* proteins that cannot be switched off and inappropriately generate proliferative signals within the cell (Byrne and Marshall, 1998). While RAS mutations occur frequently in *de novo* AML, they are generally less commonly seen in t-MDS/t-AML. As shown in Table 6, they were only seen in 14 of the 140 patients in the Copenhagen cohort (Christiansenet al., 2005; Pedersen-Bjergaardet al., 2008). Some patients that lack *RAS* mutations still exhibit an overexpression of *RAS* genes, and this has been considered as further evidence for the involvement of dysregulated *RAS* signaling in leukemogenesis (Byrne and Marshall, 1998). Interestingly, an elevated expression of the N-*RAS*

oncogene (as well as the *TP53* tumor suppressor gene) was reported in the lymphocytes of two small groups of ethylene oxide-exposed hospital nurses (Emberet al., 1998a, b).

Mutations in the *TP53* tumor suppressor gene have also been detected in a subset of t-MDS/t-AML patients. For example, 34 of the 140 patients in the Copenhagen cohort exhibited *TP53* mutations (Pedersen-Bjergaardet al., 2008). These were typically seen in patients whose leukemia cells exhibited a loss of all or part of chromosomes 5 and 7.

In its recent evaluation (Baanet al., 2009; IARC, 2009), the IARC working group indicated that "there is *limited evidence* in humans for a causal association of ethylene oxide with lymphatic and haematopoietic cancers (specifically lymphoid tumors, i.e., non-Hodgkin lymphoma, multiple myeloma, and chronic lymphocytic lymphoma)…." It should be noted that ANLL was not one of the lymphohematopoietic cancers that was considered by the IARC working group to be associated with ethylene-oxide exposure. As a result, the information on t-AML presented above, while valid for other types of alkylating agents, may not be relevant in this case. As seen in Table 7, the three lymphohematopoietic cancers mentioned by IARC have generally not been associated with other alkylating agents with the exception of butadiene, which has been associated with CLL and NHL (described below). It should also be noted that the three types of neoplasm listed by IARC originate in mature B lymphoid cells, which is also somewhat unusual for alkylating agent-related cancers.

8.3. 1,3-BUTADIENE (summarized largely from IARC, 1999, 2008a)

Butadiene is a widely used industrial chemical that has been shown to induce cancer in mice, rats, and humans. Butadiene is metabolized to a number of epoxide metabolites (stereoisomers of epoxybutene, epoxybutanediol, and diepoxybutane) that can react directly with DNA. The most common DNA adduct detected in mice and rats is the *N*7-guanine adduct (*N7*-trihydroxybutylguanine), which is derived from either epoxybutanediol or diepoxybutane. Other adducts at base-pairing sites that can be formed from the epoxide metabolites of butadiene include adducts at the *N*3-cytosine, *N*1-adenine, *N*6-adenine, *N*1-guanine, and *N*2-guanine. Crosslinks between *N*7-guanines have been detected in the liver and lungs of butadiene-treated mice. The butadiene epoxide metabolites can also be metabolized to non-DNA reactive products by glutathione-*S*-transferases and epoxide hydrolases. In the classification scheme in Vogelet al., 1998, butadiene through its diepoxybutane metabolite was considered a Category 3 agent,

which would be expected to be a potent mutagen and carcinogen. However, it was suggested by Vogel et al. (1998) that because the DNA crosslinks formed by diepoxybutane are primarily intrastrand crosslinks that are more readily repaired, diepoxybutane is a much weaker mutagen and carcinogen than other Category 3 agents. Metabolic factors are also likely to contribute to butadiene's reduced potency in rats (and probably humans). However, it should be noted that butadiene is readily bioactivated in mice and is a potent carcinogen in that species.

Butadiene and its epoxide metabolites have been shown to be genotoxic and mutagenic in most experimental systems both in vitro (with metabolic activation for butadiene) and in vivo. Butadiene exhibited clastogenic effects in mice inducing chromosomal aberrations, micronuclei, and SCEs. Similar effects were not seen in rats, and this is believed to be due to metabolic differences between the two species. Butadiene has also been shown to induce mutations with bioactivation in mammalian cells and in vivo in mice. It should be noted that considerably fewer studies of the genotoxicity of butadiene have been conducted in rats as compared to mice. The genotoxicity of the epoxide metabolites has also been extensively studied. Not surprisingly given its bifunctional nature, the diepoxybutane is the most potent of the three metabolites. For example, when monoepoxybutene, diepoxybutane, and 3,4-epoxy-1,2-butanediol were tested for mutagenicity at *HPRT* and *TK* loci in the TK6 human lymphoblastoid cells (Cochrane and Skopek, 1993; Cochrane and Skopek, 1994), all three epoxides were mutagenic, but the mutagenicity of the diepoxybutane was much greater than that seen for the other two epoxides. However, as noted by IARC (2008a), while genotoxicity studies have indicated that diepoxybutane is the most genotoxic of the epoxides formed from butadiene, the relative contribution of the various epoxide metabolites to the mutagenicity and carcinogenicity of butadiene is not known as the monoepoxybutene metabolite is likely to be formed in greater quantities.

Using either conventional techniques or new molecular cytogenetic techniques such as fluorescence in situ hybridization with DNA probes, increased frequencies of chromosomal aberrations have not generally been seen in the peripheral blood lymphocytes of butadiene-exposed workers. Exposure to butadiene has also not been associated with myelotoxicity in exposed humans.

Mutations in the cancer-related K-*Ras*, H-*Ras*, *Tp53*, *p16*/*p15*, and b-*catenin* genes have been detected in tumors of mice exposed to butadiene. K-R*as* mutations, frequently a G-to-C

transversion at codon 13, have been seen in hemangiosarcomas, lymphomas, and cancers of the lung, forestomach, and mammary tumors of butadiene-treated mice. Mutations in the *Tp53* tumor-suppressor gene have been detected in mouse lymphomas, brain tumors, and mammary gland tumors. Similarly, mutations in the *p15* and *p16* tumor suppressor genes were seen in induced lymphomas, and mutations in b-*catenin* were seen in the mammary gland tumors. The prevalence of mutations in these cancer-related genes provides strong evidence for a mutagenic mechanism in butadiene carcinogenesis. As indicated above, mutations in the *RAS* and *TP53* genes have been seen in *de novo* leukemias and t-AMLs seen in humans.

In its 2008 evaluation (IARC, 2008a), IARC concluded

> Overall, the epidemiological studies provide evidence that exposure to butadiene causes cancer in humans. … This conclusion is primarily based on the evidence for a significant exposure–response relationship between exposure to butadiene and mortality from leukaemia in the University of Alabama in Birmingham study, which appears to be independent of other potentially confounding exposures. It is also supported by elevated relative risks for non-Hodgkin lymphoma in other studies, particularly in the butadiene monomer production industry. The Working Group was unable to determine the strength of the evidence for particular histological subtypes of lymphatic and haematopoietic neoplasms because of the changes in coding and diagnostic practices for these neoplasms that have occurred during the course of the epidemiological investigations. However, the Working Group considered that there was compelling evidence that exposure to butadiene is associated with an increased risk for leukaemias.

The most recent IARC evaluation (Baanet al., 2009; IARC, 2009) did not provide additional clarification on the histological subtypes, stating that "there is sufficient evidence in humans for the carcinogenicity of 1,3-butadiene" and that "butadiene causes cancer of the haematolymphatic organs." Assuming that the earlier diagnoses were correct, the types of leukemias in the University of Alabama study that showed significant dose-related associations with butadiene exposure were CLL and CML. Increases in other NHLs such as reticulosarcoma and endothelioma seen in other studies were also provided as supportive evidence. Neither of these two types of leukemia has been commonly seen in leukemias induced by most other alkylating agents (see Table 7). It should be noted that increases in CLL and NHL have been reported with ethylene oxide exposure.

8.4. FORMALDEHYDE (summarized primarily from IARC, 2006, unless otherwise indicated)

Formaldehyde is a common industrial chemical, an environmental contaminant, and an endogenous metabolite. It has been shown to induce cancer in rats and humans. Formaldehyde is a reactive chemical that primarily binds to sulfhydryl and amine groups in polypeptides and proteins. However, it can also form DNA-protein crosslinks, which have been shown to be associated with its cytotoxic and genotoxic effects. It has also been shown to bind weakly to DNA forming monoadducts and DNA-DNA crosslinks (Lu et al., 2010). Formaldehyde also binds readily to reduced glutathione, forming a hemithioacetal that can be converted to formate by formaldehyde dehydrogenase.

Formaldehyde has exhibited genotoxic and mutagenic effects in a large number of experimental systems. *In vitro*, it has been shown to induce mutations in bacteria and mammalian cells, DNA-protein crosslinks and strand breaks, and chromosomal aberrations. In rodent models, it has been shown to induce DNA adducts, DNA-DNA and DNA-protein crosslinks, chromosome aberrations, and micronuclei, primarily at the site of exposure. Genetic damage has not typically been seen in the bone marrow or other locations distal from the site of exposure. Occasional reports of systemic effects are found in the literature, but these have not been seen in most studies.

One of the tumor types induced by formaldehyde in rats is squamous-cell nasal carcinoma. *Tp53* mutations were seen in 5 of 11 carcinomas isolated from the formaldehyde-exposed rats. However, because the types of mutation seen in the nasal tumors differed from those seen in other model systems, the principal author of the study suggested that the observed mutations may have been due to an indirect effect, possibly occurring as a result of inflammation and regenerative cell proliferation in the nasal passages of the exposed rats (Recio, 1997).

Formaldehyde-exposed workers have been reported to exhibit increased frequencies of DNA-protein crosslinks in their peripheral blood lymphocytes. Increased frequencies of micronuclei were reported to occur in the nasal and oral mucosa of formaldehyde-exposed workers but were not seen in the oral mucosal cells of volunteers exposed to variable levels of formaldehyde under controlled exposure conditions (Speitet al., 2007). Similarly, while negative results were reported in some studies, others have reported that formaldehyde-exposed workers had increased frequencies of structural chromosome aberrations and SCEs in their peripheral

blood lymphocytes (IARC, 2006; Zhanget al., 2009). Formaldehyde exposure has not typically been associated with hematotoxicity in humans (or animals). The mixed results seen in the various studies may be explained, in part, by differences in exposure levels. Recently, a biomonitoring study was conducted on a group of Chinese workers with particularly high formaldehyde exposures (median 8-hour time weighted average exposure level of 1.28 ppm [Zhanget al., 2010]). The researchers found that the exposed workers had lower blood cell counts and that peripheral stem/progenitor cells obtained from the workers exhibited elevated frequencies of monosomy for chromosome 7 and trisomy for chromosome 8—cytogenetic alterations commonly seen in human leukemias.

In its 2006 evaluation of formaldehyde (IARC, 2006), the working group concluded that "there is *sufficient evidence* in humans for the carcinogenicity of formaldehyde" based on the occurrence of nasopharyngeal cancer. With regards to leukemia, the working group concluded that "there is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde." They felt at that time that it was "not possible to identify a mechanism for the induction of myeloid leukaemia in humans by formaldehyde." In the more recent 2009 evaluation (Baanet al., 2009; IARC, 2009), the new working group concluded that "the epidemiological evidence on leukaemia has become stronger, and new mechanistic studies support a conclusion of *sufficient evidence* in humans. This highlights the value of mechanistic studies, which in only 5 years, have replaced previous assertions of biological implausibility with new evidence that formaldehyde can cause blood-cell abnormalities that are characteristic of leukaemia development." However, it should be noted that this conclusion was controversial as the working group was almost evenly split on the evaluation, with a slight majority seeing the evidence as *sufficient* for carcinogenicity, and the minority viewing the evidence as *limited*. A recent compilation and meta-analysis of formaldehyde-induced leukemia studies have indicated that formaldehyde exposure is most closely associated with myeloid leukemias, primarily AML (Zhanget al., 2009).

9. RISK ASSESSMENT IMPLICATIONS

As indicated above, approximately 25% of the agents established by IARC as human carcinogens induce lymphohematopoietic cancers, and approximately 22% are associated with the induction of leukemia, primarily AML. These agents have a wide variety of uses, and given their established carcinogenic effects, they have been the focus of many risk assessments and safety evaluations. For some of these carcinogens such as benzene or ionizing radiation, these assessments and their refinements have been ongoing for decades and involve large amounts of information. The sections below focus on how mechanistic information on these carcinogenic agents can be used to inform risk assessment decisions. The following discussion is not intended to be comprehensive but rather will focus on some key issues related to contemporary risk assessment discussions. .

9.1. HAZARD IDENTIFICATION

Hazard identification is the process by which hazardous substances—carcinogenic agents in this case—are identified and characterized. According to the IARC Preamble (IARC, 2008d), which describes the IARC groupings and the weight-of-evidence decision-making process, the Group I category "is used when there is *Sufficient Evidence of Carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *Sufficient Evidence of Carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity." Ethylene oxide represents one of the exceptional agents, which was classified based on less than sufficient evidence in humans but with sufficient evidence in animals.

The Group 2A agents represent chemicals that are probable human carcinogens for which there "is *Limited Evidence of Carcinogenicity* in humans and *Sufficient Evidence of Carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *Inadequate Evidence of Carcinogenicity* in humans and *Sufficient Evidence of Carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *Limited Evidence of Carcinogenicity* in humans.

An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A." Most of the Group 2A agents listed in Table 8 have mechanisms of action such as mutagenicity that are commonly associated with carcinogenesis. However, they have not been adequately studied in humans, or for many of the chemotherapeutic agents, they were administered in combination therapy often with other carcinogenic agents so that the carcinogenic effects for the agent being investigated cannot be separately identified.

For most of the evaluations, studies of cancer in humans and animals have played the primary role in the IARC classification. Information on the mechanism of action has typically only played a supportive role. As a result, it is reasonable to examine information on the mechanisms of action of the Group 1 and 2A carcinogens to help identify carcinogens and improve the hazard identification process. Below are several observations about how mechanistic information has and may be used in hazard identification for leukemia-inducing agents.

9.1.1. Utility of Short-Term Genotoxicity Tests

As seen in Table 8, most of the agents identified by IARC as human carcinogens are likely to act through a mutagenic mode of action. The majority of the Group 1 and 2A carcinogens are alkylating agents, but other classes of genotoxic agents such as topoisomerase II inhibitors or nucleotide analogs are also present. The majority of the Group 1 and 2A leukemia- and lymphoma-inducing agents are active in short-term tests both in vitro (with metabolic activation as needed) and in vivo (IARC, 1987a). This is not surprising given their mechanisms of action. The exceptions to this tend to be the infectious agents and the immunosuppressive agents that act through nongenotoxic or indirect genotoxic mechanisms of action.

As also shown in Table 7, most of the leukemia-inducing agents have been shown to induce chromosomal aberrations or micronuclei in the peripheral blood lymphocytes of exposed humans (and animals). In addition, at commonly used and frequently high doses, these agents also cause significant bone marrow toxicity with noticeable decreases in blood cell counts of the exposed individuals. There are a few Group 1 agents that are exceptions and do not manifest these particular patterns. Ethylene oxide and butadiene have not been reported to induce hematotoxicity in humans, and butadiene has not been shown to induce structural chromosome

aberrations in exposed workers. These two are also somewhat unusual in that the types of cancers associated with their exposure are CLL and NHL, neoplasms that originate in mature B lymphoid cells.

9.1.2. Usefulness of Animal Bioassays

There is substantial evidence to indicate that chronic animal bioassays are effective in detecting human carcinogens. As described in the IARC Preamble (IARC, 2008d), "all known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species." However, as further noted in the Preamble, "although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there are *Sufficient Evidence of Carcinogenicity* in experimental animals also present a carcinogenic hazard to humans." Accordingly, the vast majority of the Group 1 leukemia- and lymphoma-inducing agents shown in Table 7 have been reported previously to be carcinogenic in rodent bioassays (Eastmond, 1997). Indeed, many of them have been shown to induce leukemias or lymphomas in mice and in rats. Most of these have been shown to occur in mice and were T-cell leukemias or lymphomas, rather than the ANLL, which is prevalent in humans. As a result, there appears to be fundamental differences between the types of lymphohematopoietic tumors induced in humans and rodents. The reason for this remains unknown but may be related to species differences in hematopoiesis and/or immune surveillance (Eastmond, 1997).

The good correlation seen for animals and humans mentioned above was based primarily on the results for chemical carcinogens and probably does not hold for many of the infectious agents, which are likely to only infect humans and closely related species. In addition, it is not clear at this point if this correlation will hold true for the topoisomerase II inhibitors, as most of them have not been adequately tested in experimental animals. While the fusion gene products have clearly been shown to affect hematopoiesis and can cause leukemias in mice (Corralet al., 1996; Dobsonet al., 1999; Lavauet al., 2000; Forsteret al., 2003; Soet al., 2003), it is not certain if the genes are located in regions in the rodents that will allow the same chimeric genes to be formed. It should also be noted that the Group 2A carcinogens are also positive in rodent

bioassays; however, this is to be expected, as this characteristic is one of the primary reasons that the chemicals have been listed.

9.1.3. Combining Different Types of Lymphohematopoietic Cancers for Analysis

In evaluating epidemiological studies, a decision has to be made about which specific types of disease should be combined for the analysis. Often the reporting of leukemias has been grouped into the four common categories of AML, CML, ALL, and CLL. Similarly, the lymphomas and myelomas have been grouped into NHL (lymphosarcoma, reticulosarcoma, and other malignant neoplasms of lymphoid and histocytic tissue), Hodgkin's disease, and multiple myeloma (MM). More recent case-control studies of lymphoma have expanded the NHL grouping to include CLL, or to group lymphomas by cell type or by specific International Classification of Disease-Oncology category (e.g., diffuse lymphatic B-cell lymphoma, follicular lymphoma, etc.). However, many different types of groupings have been used in analyzing epidemiological data, primarily reflecting the classification system in use at the time of diagnosis or cause of death. An illustration of the various types of groupings used for studies of benzene has been described by (Savitz and Andrews, 1997). In addition, evaluations of the induction of lymphohematopoietic diseases by an agent over time can be challenging due to changes in diagnosis, the names of diseases, and classification schemes, as well as lack of detailed case and exposure information. Other issues such as misclassification errors and insufficient information on death certificates can also influence the outcome of the studies. The decision about how to analyze the data can also have a significant influence on the outcome of the analysis and the conclusions of the study.

As illustrated in Tables 1−3, there are a large number of distinct lymphohematopoietic cancers. By analyzing each separately, a study would only have the power to detect cancers that were very strongly associated with exposure to an agent if detection was even possible. In addition, the large number of comparisons could lead to some associations being labeled as significant due simply to random chance. As a result, it is common to combine specific lymphohematopoietic cancers for analysis. The key question, which has not fully been answered, is which categories of specific cancer should be combined for analysis. The value of combining uncommon lymphohematopoietic cancers has been demonstrated by Savitz and Andrews for benzene (Savitz and Andrews, 1996; Savitz and Andrews, 1997). Benzene

exposure is strongly associated with ANLL. However, its association with lymphoid cancers has been a source of ongoing discussion. Savitz and Andrews showed that by analyzing non-AML cancers together, a significant association between benzene exposure and these cancers could also be shown. IARC, in its most recent evaluation, has given more credence to an association between benzene and other lymphohematopoietic cancers as it concluded that there was evidence, albeit limited, for an association between benzene and ALL, CLL, NHL, and multiple myeloma (Baanet al., 2009; IARC, 2009). These results suggest that benzene can target the hematopoietic stem and progenitor cells as well as more mature lymphoid cells.

In addition to combining specific types of cancers for analysis during individual studies, it may be informative to see how various authoritative bodies such as IARC, the National Academies of Science Biological Effects of Ionizing Radiation (BEIR) committee, and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) have combined the lymphohematopoietic cancers in making decisions about risk or for weight-of-evidence determinations for various leukemogenic agents. As indicated above for benzene, IARC chose to evaluate the major types of cancer separately. However, it is likely that the association between benzene and one type of cancer provided supportive evidence that benzene could be associated with another type of lymphohematopoietic cancer. This type of supporting evidence appears to have played an important role in the evaluations of butadiene where associations with CML, CLL, and to some degree, NHL, were combined in concluding that butadiene exposure caused cancer of the "haematolymphatic organs." Similarly, information on associations with different types of lymphohematopoietic cancers contributed to the recent IARC evaluation on formaldehyde (AML and CML) and ethylene oxide (NHL, MM, and CLL). It should be noted that for butadiene and probably benzene, supportive evidence came from associations with both myeloid and lymphoid tumors.

In recent evaluations of ionizing radiation, it has been common to use all leukemias or combine the results for ALL, AML, and CML in modeling the data and assessing cancer risks (UNSCEAR, 2000a,b; NRC, 2006 and references therein). Increases in CLL have not been seen in radiation-exposed study groups. When presenting the study results, the radiation-induced leukemias are frequently described in various documents as simply leukemias or non-CLL leukemias.

Thus, as illustrated in the evaluation of the various cancer-inducing agents, there is no strict consensus on how specific lymphohematopoietic cancers should be combined for analysis and weight-of-evidence determinations. As discussed above, a variety of combinations including those combining acute and chronic myeloid neoplasms as well as lymphoid and myeloid neoplasms have been used in recent evaluations.

9.1.4. Potential Influence of Latency Period in Identifying Leukemogens

The period between the initial exposure to a carcinogenic agent and the onset of cancer is known as the latency period. Latency periods for leukemias tend to be much shorter than those seen for other induced cancers such as lung cancer induced by tobacco smoke, which has a median latency period of approximately 30 years (Weiss, 1997). As indicated above, the latency period for topoisomerase II inhibitors is quite short with median latency periods of 2−3 years. For radiation and chemical chemotherapy agents, the induced leukemias first appear 1−2 years after the beginning of treatment. The median incidence peaks at about 4−7 years, and by 10−15 years after the beginning of treatment, the incidence has frequently declined to control or near control levels (Casciato and Scott, 1979; Pedersen-Bjergaardet al., 1987; Kaldoret al., 1990; Davies, 2000; Schonfeldet al., 2006). This indicates that for leukemogens such as the chemotherapeutic alkylating agents, the risk of developing t-AML will most likely peak at ~4−7 years after the beginning of exposure and will begin to decline with additional follow-up. Continuing follow-up beyond 10 to 15 years after treatment would be expected to significantly reduce associations between exposure and leukemia and cause a bias in results towards no effect. Hence, adding person-years after exposure ends or is substantially reduced, as sometimes occurs in occupational studies, may significantly weaken true associations between exposure and the incidence of leukemia. The influence of latency or time since first exposure has been clearly demonstrated for benzene (Rinskyet al., 2002; Silveret al., 2002) and has been postulated to have had an influence on recent formaldehyde results (Beane Freemanet al., 2009). Failure to account for latency period for weak carcinogens or under conditions of modest exposure for potent carcinogens could reduce the association so that the agent or exposure would no longer be considered carcinogenic. One note of caution is that the described latency periods have typically been seen with high doses of the leukemia-inducing agents. There is evidence that the latency

period can be significantly influenced by the administered dose with higher doses producing shorter latency periods and lower doses producing longer latency periods (Cadmanet al., 1977).

9.1.5. Metabolism and Bioactive Dose at the Target Organ

One of the fundamental principles of toxicology is that the toxicological response is related to the dose of the bioactive agent in the target tissue. However, the tissue dose of the bioactive agent may differ significantly from the external exposure dose. For many carcinogens, even if exposure occurs, the chemical may not arrive at the target organ in a form that enables it to exert a toxic or mutagenic effect due to pharmacokinetic or metabolic reasons. In fact, this is a fundamental difference between the risk assessment of ionizing radiation and chemical leukemogens. Because of its ability to directly penetrate tissues, radiation risk estimates are almost always based on the dose of radiation that reaches the bone marrow. In contrast, risks for chemical leukemogens such as benzene, butadiene, or ethylene oxide are typically based on the exposure dose and may not accurately reflect the bioactive dose that reaches the bone marrow.

Studies have also shown that pharmacokinetic and metabolic factors can significantly influence the risks from leukemia-inducing agents. For example, the peak plasma concentrations of melphalan have been shown to vary by over 50-fold after oral dosing due to variability in absorption, first pass metabolism, and rapid hydrolysis (GlaxoSmithKline, 2007). Indeed, for a few patients, detectable plasma levels of melphalan were not seen even after the administration of a high dose (1.5 mg/kg) of the drug (Choi et al., 1989). The differences in plasma concentration would undoubtedly have an effect on its efficacy as well as its risk of inducing t-AML.

Metabolism has been shown to exert a major effect on the mutagenic and carcinogenic risks of leukemia-inducing agents. For example, as discussed earlier, ethylene oxide is highly genotoxic and mutagenic in vitro. Yet, in vivo, it is a relatively weak mutagen and carcinogen as compared to other alkylating agents (Vogel et al., 1998). It should be noted that most of the alkylating agents used for comparison were antineoplastic drugs designed to be highly toxic. This is likely due to the efficient metabolism of the reactive epoxide by epoxide hydrolases, glutathione transferases, and other detoxification enzymes as well as efficient repair of the induced adducts. Similarly, bioactivation of leukemogens such as butadiene, benzene, and

cyclophosphamide to their reactive metabolites has been shown to significantly influence the toxicity and genotoxicity of these agents.

9.1.6. DNA-Adduct Type, Metabolism, and Repair

The type of DNA adducts formed and their repair can have a major impact on the toxicity, mutagenicity, and probably the cancer risk of leukemia-inducing agents. As indicated earlier, three major classes of alkylating agents have been identified that have significantly different mutagenic and carcinogenic potencies (Vogelet al., 1998). Category 1 agents were mono-functional alkylating agents such as ethylene oxide and methyl methane sulfonate, which primarily react at the N7 and N3 moieties of purines in DNA. These adducts are efficiently repaired, and as a result, these agents tend to be relatively weak mutagens and carcinogens with higher doses associated with observed increases in tumors in animals. Category 2 agents such as procarbazine and ENU induce *O*-alkyl adducts and *N*-alkyl adducts in DNA, which are often involved in base pairing and are slowly repaired. These agents are generally potent mutagens and carcinogens. Category 3 agents such as melphalan and busulfan induce DNA breaks and structural aberrations through their ability to cross-link DNA. They are highly toxic, mutagenic, and carcinogenic. As indicated above, butadiene can be metabolized to diepoxybutane, a cross linking agent, so it is classified as a Category 3 agent. However, its potency for rats and probably humans has been reported to be much lower that the other Category 3 agents. This is probably due to the need for metabolism as indicated above as well as the nature of the adducts formed by butadiene. The butadiene crosslinks tend to be intrastrand and are more efficiently repaired. Consistent with this explanation is the fact that diepoxybutane is believed to be the reactive intermediate formed from treosulfan, a chemotherapeutic agent that appears to be somewhat less potent in inducing t-AML in humans than other Category 3 chemotherapeutic agents when considered on a mg/kg-basis (Kaldoret al., 1990). Interestingly, it should be noted that treosulfan administration to humans has been associated with AML whereas occupational exposure to 1,3-butadiene has been associated with CLL and CML. One possible explanation is that the epoxybutene metabolite may play a more important role than diepoxybutane in inducing the butadiene-related leukemias in humans.

9.1.7. Individual Susceptibility

Many factors such as age, sex, genetic composition, and general health status have been shown to influence susceptibility to leukemia-inducing agents. For example, age has been shown to be a factor in susceptibility to radiation-induced leukemia. Studies of the atomic bomb survivors, who were exposed to both *gamma*, and to a lesser extent, neutron radiation, indicated that the highest leukemia risks were seen in children (Prestonet al., 1994, 2004). The leukemia risk also decreased more rapidly in children as compared to those in older age groups (Prestonet al., 1994). Interestingly, a similar increased susceptibility has not been seen for children treated with alkylating agent-based chemotherapy as their leukemia risks do not appear to be greater than those seen in adults, and in some cases, may be less (Levine and Bloomfield, 1992; Pyattet al., 2005, 2007). However, direct comparisons are difficult as in most studies children and adults have been treated with different therapeutic regimens. For the nontherapeutic classes of leukemia-inducing agents, little is known about the relative susceptibility of children to leukemia, as the critical studies have almost always been conducted on adults. However, a number of studies on related biomarkers have indicated that children or adolescents are also susceptible to the toxic and genotoxic effects of these leukemogenic chemicals (Aksoyet al., 1974; Aksoy, 1988; Niazi and Fleming, 1989; Neriet al., 2006).

Genetic polymorphisms in genes coding for xenobiotic metabolizing enzymes, DNA-metabolizing or repair enzymes, and drug transporter proteins are other factors that have been implicated as significantly influencing an individual's risk of developing leukemia when exposed to genotoxic agents. A considerable number of studies have been conducted to identify enzymes involved in the bioactivation and the inactivation of carcinogenic agents (for reviews, see Cheoket al. [2006], Leoneet al. [2007, 2010], and Guillem and Tormo [2008]). As discussed above and in the review articles, significant associations have been seen for a number of genes coding for xenobiotic metabolizing enzymes, DNA-metabolizing and repair enzymes, and drug transporters. Individuals with genes coding for nonfunctional or less active copies of various glutathione-*S*-transferases, CYP3A4, and NQO1 have been reported to be at increased risk for developing t-AML following chemotherapy. Similar increased risks have been seen for individuals that lack efficient DNA-metabolizing or repair enzymes such as enzymes involved in nucleotide excision repair or mismatch repair. However, further research in this area is needed as similar associations for the metabolizing enzymes and DNA-repair enzymes have not been

seen in other studies. As discussed by Lutz and colleagues, from a population risk perspective, the increased susceptibility associated with the various genetic polymorphisms can have a significant impact on cancer risks, particularly among those exposed to lower doses (Lutz, 1990, 2001).

9.1.8. Summary

As evident from Table 8 and from the above discussion, leukemia-inducing agents act through different mechanisms to induce their carcinogenic effects. While most of these are likely to act through a mutagenic mode of action, different leukemogens have different potencies and different associated risks, which appear to be significantly influenced by the specific mechanisms involved. Even among the alkylating agents, different chemicals can have different potencies that are likely due to the nature of the DNA adducts formed and their repair as well as metabolic and pharmacokinetic factors. In addition, polymorphisms in genes related to xenobiotic metabolism and DNA repair can lead to increased susceptibility among groups in the population.

Table 1. Simplified classification of the major lymphohematopoietic neoplastic diseases in humans based largely on the French-American-British (FAB) classification

I.	Neoplasms of multipotent stem cell origin	
	Chronic myelogenous leukemia	CML
II.	Neoplasms possibly originating in the multipotent stem cell	
	Myelodysplastic syndromes	MDS
	Refractory anemia	RA
	Refractory anemia with ring sideroblasts	RARS
	Refractory anemia with excess blasts	RAEB
	Chronic myelomonocytic leukemia	CMML
	Refractory anemia with excess blasts in transformation	RAEB
	Chronic myeloproliferative disorders	
III.	Neoplasms originating in stem cells or myeloid-committed precursors	
	Acute myeloid leukemia or acute nonlymphocytic leukemia	AML/ANLL
	Acute myeloblastic leukemia with minimal differentiation	M0
	Acute myeloblastic leukemia without maturation	M1
	Acute myeloblastic leukemia with maturation	M2
	Acute promyelocytic leukemia	M3
	Acute myelomonocytic leukemia	M4
	Acute monocytic leukemia	M5
	Acute erythroleukemia	M6
	Acute megakaryoblastic leukemia	M7
	Malignant histiocytosis	
IV.	Neoplasms of lymphoid-committed precursors	
	Immature phenotype: Acute lymphoblastic leukemia	ALL, L1,L2
	B-cell lineage	b-ALL
	T-cell lineage	t-ALL
	Intermediate or mature phenotype: non-Hodgkin's lymphoma	NHL
	Nodal/splenic phase	
	Leukemic phase	
	B-cell lineage	
	non-Burkitt's	
	Burkitt's	L3
	T-cell lineage	
	Lymphoblastic lymphoma	
	Adult T-cell leukemia/lymphoma	
	Mature lymphocytic phenotype	
	Prolymphocytic leukemia	
	Chronic lymphocytic leukemia	CLL
	B-cell lineage	
	T-cell lineage	
	Hairy cell leukemia	
	Plasmacytoid phenotype: Marrow-phase predominant	
	Macroglobulinemia	

Heavy chain diseases
Myeloma
Hodgkin's Lymphoma

Adapted from Sullivan (1993).

Table 2. WHO classification of myeloid and related neoplasms

MYELOPROLIFERATIVE NEOPLASMS (MPNs)
- Chronic myelogenous leukemia, *BCR-ABL1*–positive
- Chronic neutrophilic leukemia
- Polycythemia vera
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic eosinophilic leukemia, not otherwise specified
- Mastocytosis
  - Cutaneous mastocytosis
  - Systemic mastocytosis
  - Mast cell leukemia
  - Mast cell sarcoma
  - Extracutaneous mastocytoma
- Myeloproliferative neoplasms, unclassifiable

MYELOID AND LYMPHOID NEOPLASMS ASSOCIATED WITH EOSINOPHILIA AND ABNORMALITIES OF *PDGFRA*, *PDGFRB*, OR *FGFR1*
- Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
- Myeloid neoplasms with *PDGFRB* rearrangement
- Myeloid and lymphoid neoplasms with *FGFR1* abnormalities

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS (MDS/MPN)
- Chronic myelomonocytic leukemia
- Atypical chronic myeloid leukemia, *BCR-ABL1*–negative
- Juvenile myelomonocytic leukemia
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable
- *Refractory anemia with ring sideroblasts and thrombocytosis (provisional entry)*

MYELODYSPLASTIC SYNDROME (MDS)
- Refractory cytopenia with unilineage dysplasia
  - Refractory anemia
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anemia with excess blasts
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
- Childhood myelodysplastic syndrome
- *Refractory cytopenia of childhood (provisional entry)*

ACUTE MYELOID LEUKEMIA AND RELATED NEOPLASMS
- **Acute myeloid leukemia with recurrent genetic abnormalities**
  - AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*

AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
APL with t(15;17)(q22;q12); *PML-RARA*
AML with t(9;11)(p22;q23); *MLLT3-MLL*
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21;q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
AML with mutated NPM1 (provisional entry)
AML with mutated CEBPA (provisional entry)

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukemia, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Acute erythroid leukemia
Pure erythroid leukemia
Erythroleukemia, erythroid/myeloid
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

ACUTE LEUKEMIAS OF AMBIGUOUS LINEAGE
Acute undifferentiated leukemia
Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*
Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
Mixed phenotype acute leukemia, B-myeloid, NOS
Mixed phenotype acute leukemia, T-myeloid, NOS
Natural killer (*NK*) *cell lymphoblastic leukemia/lymphoma (provisional entry)*

Source: WHO (2008).

Table 3. WHO classification of lymphoid neoplasms

PRECURSOR LYMPHOID NEOPLASMS

B lymphoblastic leukemia/lymphoma

B lymphoblastic leukemia/lymphoma, NOS
B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2);*BCR-ABL 1*
B lymphoblastic leukemia/lymphoma with t(v;11q23);*MLL* rearranged
B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) *TEL-AML1* (*ETV6-RUNX1*)
B lymphoblastic leukemia/lymphoma with hyperdiploidy
B lymphoblastic leukemia/lymphoma with hypodiploidy
B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) *IL3-IGH*
B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*

T lymphoblastic leukemia/lymphoma

MATURE B-CELL NEOPLASMS

Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable (provisional entry)
  Splenic diffuse red pulp small B-cell lymphoma (provisional entry)
  Hairy cell leukemia—variant (provisional entry)
Lymphoplasmacytic lymphoma
  Waldenstrom macroglobulinemia
Heavy chain diseases
  Alpha-heavy chain disease
  Gamma-heavy chain disease
  Mu heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
Nodal marginal zone B-cell lymphoma
Pediatric nodal marginal zone lymphoma (provisional entry)
Follicular lymphoma
Pediatric follicular lymphoma (provisional entry)

Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), NOS
  T-cell/histiocyte-rich large B-cell lymphoma
  Primary DLBCL of the CNS

Primary cutaneous DLBCL, leg type
EBV positive DLBCL of the elderly (provisional entry)
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK-positive large B-cell lymphoma
Plasmablastic lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
Primary effusion lymphoma
Burkitt lymphoma/leukemia
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkett lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

MATURE T-CELL AND NK-CELL NEOPLASMS

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells (provisional entry)
Aggressive NK-cell leukemia
Systemic EBV-positive T-cell lymphoproliferative disease of childhood
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30-positive anaplastic large cell lymphoma
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous CD8 positive aggressive epidermotropiccytotoxic T-cell lymphoma (provisional entry)
Primary cutaneous CD4 positive small/medium T-cell lymphoma
Peripheral T-cell lymphoma, NOS (provisional entry)
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK positive
Anaplastic large cell lymphoma, ALK positive (provisional entry)

HODGKIN LYMPHOMA

Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma

Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma

HISTIOCYTIC AND DENDRITIC-CELL NEOPLASMS

Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Indeterminate dendritic cell tumor
Disseminated juvenile xanthogranuloma

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

Early lesions
  Plasmacytic hyperplasia
  Infectious mononucleosis-like PTLD
Polymorphic PTLD
Monomorphic PTLD (B- and T/NK-cell types)
Classical Hodgkin lymphoma type PTLD

Source: WHO (2008).

Table 4. Cytogenetic comparisons of *de novo* leukemias and t-AML[a]

Cytogenetic features	AML	
	de novo **n = 3649 (%)**	**t-AML** **n = 581 (%)**
Number of anomalies		
1 anomaly	2186 (60)	242 (42)
2 anomalies	641 (18)	104 (18)
≥3 anomalies	822 (23)	235 (40)
Ploidy level		
hypodiploid	813 (22)	224 (39)
pseudodiploid	1843 (51)	242 (42)
hyperdiploid	974 (27)	108 (19)
tri-/tetraploid	13 (0.4)	7 (1.2)
unknown ploidy	6 (0.2)	0
Unbalanced anomalies	2734 (75)	491 (85)
3p-	33 (0.9)	17 (2.9)
-5	152 (4.2)	73 (13)
5q−	249 (6.8)	77 (13)
−7	340 (9.3)	167 (29)
−7 (sole)	114 (3.1)	51 (8.8)
7q−	147 (4.0)	36 (6.2)
der(1;7)	8 (0.2)	12 (2.1)
loss of 5 and/or 7	717 (20)	284 (49)
+8	614 (17)	84 (14)
+8 (sole)	269 (7.4)	19 (3.3)
11q−	82 (2.2)	17 (2.9)
der(12p)	153 (4.2)	37 (6.4)
13q−	32 (0.9)	7 (1.2)
−17	172 (4.7)	53 (9.1)
der(17p)	104 (2.9)	36 (6.2)
−18	129 (3.5)	40 (6.9)
20q−	45 (1.2)	13 (2.2)
−21	92 (2.5)	41 (7.1)
Balanced anomalies	1713 (47)	215 (37)
t(1;3)(p36;q21)	2 (0.1)	3 (0.5)
inv(3)(q21q26)[b]	26 (0.7)	1 (0.2)
t(6;11)(q27;q23)	7 (0.2)	2 (0.3)
t(6;9)(p23;q34)	18 (0.5)	1 (0.2)
t(8;16)(p11;p13)	10 (0.3)	2 (0.3)
t(8;21)(q22;q22)	335 (9.2)	11 (1.9)
t(9;11)(p22;q23)	64 (1.8)	35 (6.0)
t(9;22)(q34;q11)	52 (1.4)	0
t(11;19)(q23;p13)	16 (0.4)	14 (2.4)
t(11q23)	144 (3.9)	72 (12)
t(15;17)(q22;q12)	388 (11)	16 (2.8)
inv(16)(p13q22)[c]	144 (3.9)	4 (0.7)
t(21q22)	375 (10)	20 (3.4)

[a]Includes 'unselected' cases from the Mitelman Database of Chromosome Aberrations in Cancer.
[b]Includes also cases with t(3;3)(q21;q26).
[c]Includes also cases with t(16;16)(p13;q22).

Source: Mauritzsonet al. (2002). Reprinted by permission from the Nature Publishing Group.

Table 5. Frequency of molecular mutations in *de novo*AMLand t-MDS/t-AML[a]

Mutated gene	AML *de novo*	t-MDS/t-AML
FLT3 (ITD[b])	35%	0%
FLT3 (TKD[c])	9%	<1%
NRAS	10−15%	10%
KITD816	~5%	NA[d]
MLL (ITD[b])	3%	2−3%
RUNX1	10−15%	15−30%
TP53	10%	25−30%
PTPN11	~2%	3%
NPM1	35−50%	4−5%
CEBPA	6−15%	Rare
JAK2V617F	2−5%	2−5%

[a]From Qianet al. (2009). Reprinted with permission from Elsevier.
[b]ITD = internal tandem duplication.
[c]TKD = tyrosine kinase-domain.
[d]NA = not available.

Table 6. Gene mutations observed in the Copenhagen series of 140 patients with t-MDS (*n* = 89) or t-AML (*n* = 51)[a]

	t-MDS	t-AML
Class I mutations		
Tyrosine kinases		
FLT3 ITD+ point mutations	1	10
cKIT point mutations	0	2
cFMS point mutations	0	0
JAK2 point mutations	2	0
Genes in the RAS/BRAF pathway		
KRAS or NRAS point mutations	7	7[b]
BRAF point mutations	0	3[b]
PTPN11 point mutations	2	2
Class II mutations		
Transcription factors		
AML1/CBFB chimerically rearranged	3	7
AML1 point mutations	20	2
MLL chimerically rearranged	0	11
MLL ITD	1	1
RARA chimerically rearranged	0	2
EVI1 chimerically rearranged	3	1
CEBPA point mutations	0	0
NPM1 point mutations	3	7
Tumor suppressor gene		
TP53 point mutations	25	9
Total 131 mutations observed	67	64

[a]From Pedersen-Bjergaardet al. (2008) Reprinted with permission from the Nature Publishing Group.
[b]One patient had a mutation of KRAS together with a mutation of BRAF possibly in different subclones.

Table 7. Characteristics of selected known and probable human leukemia- and lymphoma-inducing agents

Agents carcinogenic to humans	CAS	1° Lymphohemato-poetic cancer	2° limited evidence	Myelotoxicity	Chromosomal Aberrations[a]	Source(s)
DNA-reactive						
1,3-Butadiene		Lympho-hematopoietic cancers		-[b]	-	IARC, 2008a, 2009; Baanet al., 2009
1,4-Butanediol dimethanesulfonate (Busulfan, Myleran)	55-98-1	ANLL		+	SCA	Grosseet al., 2009; IARC, 1987b
Chlorambucil	305-03-3	ANLL		+	SCA	Grosseet al., 2009; IARC, 1987b
(1-(2-)Chlorethyl)-3-(4-methylcyclohexyl) nitrosurea (Methyl-CCNU, Semustine)	13909-09-6	ANLL		+	NI[c]	Grosseet al., 2009
Cyclophosphamide	50-18-0	ANLL		+	SCA	Grosseet al., 2009; IARC, 1987b
Ethylene Oxide	75-21-8		NHL, MM, CLL	-	SCA	IARC, 2009, 2008b; Baanet al., 2009
Formaldehyde	50-00-0	Myeloid leukemias		+/-	+/-	IARC, 2009, 2006
Melphalan	148-82-3	ANLL		+	SCA	Grosseet al., 2009; IARC, 1987b
MOPP therapy		ANLL		+	SCA	Grosseet al., 2009; IARC, 1987b
Treosulfan	299-75-2	ANLL		+	NI	Grosseet al., 2009; IARC, 1987b
Thio-TEPA (tris(1-aziridinyl)-phosphine)	52-24-4	Leukemia		+	SCA	Grosseet al., 2009; IARC, 1987b
Topoisomerase II-inhibitor						
Etoposide	33419-42-0	ANLL		+	MN	Grosseet al., 2009; IARC, 2000a
Immunosuppressive agents						
Cyclosporine	79217-60-0	NHL		-	SCA	Grosseet al., 2009; IARC, 1990c
Azathioprine	446-86-6	NHL		+	SCA	Grosseet al., 2009; IARC,

						1987b
Other						
Benzene	71-43-2	ANLL	NHL, ALL, CLL, MM	+	SCA	IARC, 2009; Baanet al., 2009
2,3,7,8-TCDD	1746-01-6		NHL	-	-	IARC, 2009
X- and *Gamma*-radiation		ANLL, CML, ALL		+	SCA	IARC, 2000b
Neutron radiation			leukemia	NI	SCA	IARC, 2000b
Thorium-232 and its decay products		ANLL, CML, ALL		NI	SCA	El Ghissassiet al., 2009; IARC, 2001
Phosphorus-32, as phosphate		ANLL		+	SCA	IARC, 2001
Fission products including strontium-90		Leukemia (non-CLL)		NI	NI	El Ghissassiet al., 2009; Krestininaet al., 2010
Tobacco smoking and tobacco smoke		ANLL		NI	SCA	IARC, 2004
Tobacco smoking (parental exposure)			Childhood Leukemia (ALL)	NI	NI	Secretanet al., 2009
Rubber manufacturing occupation		Leukemia, Lymphoma		NI	SCA	IARC, 2009
Painting occupation (maternal exposure)			Childhood leukemia	NI	NI	IARC, 2009
Infectious agents						
Epstein-Barr virus		Burkitt's lymphoma, NHL NK/T-cell lymphoma, Hodgkin's lymphoma		-	NI	Bouvardet al., 2009; IARC, 1997
Human immunodeficiency virus Type 1		NHL, Hodgkin's lymphoma		+	NI	Bouvardet al., 2009; IARC, 1996a
Human T-cell lymphotrophic virus Type 1		Adult T-cell leukemia and lymphoma		-	NI	Bouvardet al., 2009; IARC, 1996b
Hepatitis C virus		NHL		-	NI	Bouvardet al., 2009
Helicobacter pylori		low-grade B-cell		-	NI	Bouvardet al., 2009

		MALT				
Kaposi's sarcoma herpes virus		1° effusion lymphoma		-	NI	Bouvardet al., 2009
Selected agents probably carcinogenic to humans (IARC Group 2A)						
DNA-reactive						
Bischloroethyl nitrosourea (BCNU; carmustine)	154-93-8		ANLL	+	NI[d]	IARC, 1987b
1-(2-)Chlorethyl-3-cyclohexyl-1-nitrosurea (CCNU; lomustine)	13010-47-4		ANLL	+	NI	IARC, 1987b
N-Ethyl-*N*-nitrosourea	759-73-9		ANLL?	NI	NI[d]	IARC, 1987b
Cisplatin	15663-27-1		leukemia	+	NI[d]	IARC, 1987b
Nitrogen Mustard (Mechlorethamine)	51-75-2		ANLL	+	SCA	IARC, 1987b
Procarbazine	671-16-9		ANLL	+	NI[d]	IARC, 1987b
Chlorozotocin	54749-90-5		ANLL	+	NI	IARC, 1990b
Topoisomerase II-inhibitor						
Adriamycin	25316-40-9		ANLL	+	SCA	IARC, 1987b
Teniposide	29767-20-2		ANLL	+	NI[d]	IARC, 2000c
Other						
Azacytidine	320-67-2		Leukemia	+	NI[d]	IARC, 1990a
Chloramphenicol	56-75-7		ANLL	+	NI	IARC, 2000c

[a]SCA = structural chromosome aberrations, MN = micronuclei.
[b]Myelotoxicity is either not seen or infrequently seen.
[c]No information located for humans.
[d]Increases seen in the blood or bone marrow of experimental animals.

Table 8. Likely mechanisms involved in the carcinogenesis of selected known and probable human leukemia- and lymphoma-inducing agents

Agents carcinogenic to humans (IARC Group 1 or similar)						
Agent	**Cancer**	**Class**	**Activation**	**1° Mechanism**	**Other**	**1° Source**
1,3-Butadiene	Various	Industrial chemical	Bioactivated to mono- and bifunctional alkylating agents	Mutation resulting from DNA binding and/or chromosomal alterations	Metabolized into diepoxybutane	IARC, 2008a, 2009; Baanet al., 2009
Busulfan (Myleran; 1,4-Butanediol dimethanesulfonate)	ANLL	Therapeutic agent	Direct-acting bifunctional alkylating agent	Mutation resulting from DNA binding and/or chromosomal alterations		Grosseet al., 2009
Chlorambucil	ANLL	Therapeutic agent	Direct-acting bifunctional alkylating agent	Mutation resulting from DNA binding and/or chromosomal alterations		Grosseet al., 2009
Semustine (Methyl-CCNU; 1-(2-Chlorethyl)-3-(4-methylcyclohexyl)1-nitrosurea)	ANLL	Therapeutic agent	Degrades to direct-acting alkylating and carbamoylating agents	Mutation resulting from DNA binding and/or chromosomal alterations		Grosseet al., 2009
Cyclophosphamide	ANLL	Therapeutic agent	Bioactivated to bifunctional alkylating agent and acrolein	Mutation resulting from DNA binding and/or chromosomal alterations		Grosseet al., 2009
Ethylene oxide	Various	Industrial chemical	Direct-acting alkylating agent	Mutation resulting from DNA binding and/or chromosomal alterations		IARC, 2008b, 2009; Baanet al., 2009
Formaldehyde	ANLL	Industrial chemical	Direct-acting, forms DNA-protein crosslinks	Unknown, possibly mutation resulting from DNA binding and/or chromosomal alterations		IARC, 2006, 2009; Baanet al., 2009
Melphalan	ANLL	Therapeutic agent	Direct-acting bifunctional alkylating agent	Mutation resulting from DNA binding and/or chromosomal alterations		Grosseet al., 2009
MOPP therapy	ANLL	Combination of therapeutic	A direct-acting bifunctional and an	Mutation resulting from DNA binding and/or		Grosseet al., 2009

		agents	indirect monofunctional alkylating agent, a microtubule inhibitor, and a glucocortocoid	chromosomal alterations		
Treosulfan	ANLL	Therapeutic agent	Converts to a mono- and bifunctional alkylating agent	Mutation resulting from DNA binding and/or chromosomal alterations	Converts into diepoxybutane, an (intrastrand?) crosslinking agent.	Hartleyet al., 1999; Grosseet al., 2009
Thio-TEPA (tris(1-aziridinyl)-phosphine)	Leukemia	Therapeutic agent	Direct-acting trifunctional alkylating agent. Also, metabolized to monofunctional alkylating agent aziridine.	Mutation resulting from DNA binding and/or chromosomal alterations		Maanenet al., 2000; Grosseet al., 2009
Etoposide	ANLL	Therapeutic agent	Topoisomerase II-poison	Mutation resulting from chromosomal breakage and translocations	Results in modified transcription factor	Grosseet al., 2009
Cyclosporine	NHL	Therapeutic agent	Inhibition of transcription factors that regulate inducible cytokine expression	Immunosuppression		Grosseet al., 2009
Azathioprine	NHL	Therapeutic agent	Metabolized into nucleotide analog	Immunosuppression	Also genotoxic	Grosseet al., 2009
Benzene	ANLL	Industrial chemical and environmental agent	Metabolized into reactive protein and DNA-binding species	Unknown, likely mutation resulting from either DNA binding, topoisomerase II-inhibition, and/or oxidative damage	Likely multiple metabolites and modes of action involved	Baanet al., 2009; IARC, 2009
2,3,7,8-TCDD	NHL[a]	Environmental contaminant	Receptor-mediated effects modifying cellular replication and apoptosis	Unknown, likely immunosuppression	Also can lead to DNA damage through oxidative stress	Baanet al., 2009; IARC, 2009; Holsappleet al., 1996

X- and *Gamma*-radiation	ANLL CML ALL	Therapeutic, energy and military uses	Direct and indirect DNA damage	Mutation resulting from DNA damage and/or chromosomal alterations		IARC, 2000b; El Ghissassiet al., 2009
Alpha and beta particle emitters	ANLL (also CML and ALL for Th-32)	Therapeutic, energy and military uses	Direct and indirect DNA damage	Mutation resulting from DNA damage and/or chromosomal alterations		IARC, 2001; El Ghissassiet al., 2009
Tobacco smoking and tobacco smoke	ANLL	Lifestyle use	Direct and indirect DNA damage	Unknown, likely mutation resulting from DNA binding and/or chromosomal alterations		IARC, 2004; Secretanet al., 2009
Tobacco smoking (parental)	Childhood ALL	Parental use	Direct and indirect DNA damage	Unknown, assumed mutation resulting from DNA binding and/or chromosomal alterations occurring in germ cells or *in utero*	Epigenetic changes could also contribute	IARC, 2004; Secretanet al., 2009
Rubber manufacturing occupation	Leukemia Lymphoma	Occupational exposure	Unknown but DNA-reactive chemicals are used	Unknown, assumed to be mutation resulting from DNA binding and/or chromosomal alterations and/or immunosuppression		IARC, 2009
Painting occupation	Childhood leukemia[a]	Occupational exposure	Unknown but DNA-reactive chemicals are used	Unknown, assumed mutation resulting from DNA binding and/or chromosomal alterations occurring in germ cells or *in utero*	Other mechanisms are also likely.	IARC, 2009
Epstein-Barr virus	Burkitt's lymphoma NHL NK/T-cell lymphoma Hodgkin's	Infectious agent	Viral infection and expression of viral proteins leading to lymphocyte transformation	Alteration in normal B-lymphocyte function leading to cell proliferation, inhibition of apoptosis, genomic instability, and cell		Hjalgrim and Engels, 2008; Bouvardet al., 2009

	lymphoma			migration		
Human immunodeficiency virus Type 1	NHL	Infectious agent	Viral infection and expression of viral proteins leading to loss of CD 4+ T lymphocytes	Immunosuppression (as an indirect effect)		Hjalgrim and Engels, 2008; Bouvardet al., 2009
Human T-cell lymphotrophic virus Type 1	Adult T-cell leukemia and lymphoma	Infectious agent	Viral infection and expression leading to lymphocyte transformation	Immortalization and transformation of T cells		Hjalgrim and Engels, 2008; Bouvardet al., 2009
Hepatitis C virus	NHL	Infectious agent	Viral infection and expression of viral proteins leading to chronic immune stimulation	Chronic immune stimulation		Hjalgrim and Engels, 2008; Bouvardet al., 2009
Helicobacter pylori	Low-grade B-cell MALT	Infectious agent	Inflammation leading to cellular alterations	Oxidative stress, altered cellular turnover and gene expression, methylation, and mutation	Chronic immune stimulation.	Hjalgrim and Engels, 2008; Bouvardet al., 2009
Kaposi's sarcoma herpes virus	1° Effusion lymphoma	Infectious agent	Viral infection and expression of viral proteins	Cell proliferation, inhibition of apoptosis, genomic instability, cell migration		Bouvardet al., 2009
Selected agents probably carcinogenic to humans (IARC Group 2A)						
Bischloroethyl nitrosourea (BCNU; carmustine)	ANLL	Therapeutic agent	Direct-acting bifunctional alkylating agent.	Mutation resulting from DNA binding and/or chromosomal alterations		IARC, 1987b; Vogelet al., 1998
(1-(2-)Chlorethyl)-3-cyclohexyl-1-nitrosurea (CCNU; lomustine)	ANLL	Therapeutic agent	Direct-acting bifunctional alkylating agent.	Mutation resulting from DNA binding and/or chromosomal alterations		IARC, 1987b; Vogelet al., 1998
N-Ethyl-*N*-nitrosourea	ANLL?	Experimental reagent	Direct-acting alkylating agent	Mutation resulting from DNA binding and/or chromosomal alterations		IARC, 1987b; Vogelet al., 1998

Cisplatin	Leukemia	Therapeutic agent	Direct-acting bifunctional DNA binding agent.	Mutation resulting from DNA binding and/or chromosomal alterations		IARC, 1987b; Vogelet al., 1998
Nitrogen Mustard (Mechlorethamine)	Leukemia	Therapeutic agent	Direct-acting bifunctional alkylating agent.	Mutation resulting from DNA binding and/or chromosomal alterations		IARC, 1987b; Vogelet al., 1998
Procarbazine	ANLL	Therapeutic agent	Bioactivated to a monofunctional alkylating agent.	Mutation resulting from DNA binding and/or chromosomal alterations		IARC, 1987b; Vogelet al., 1998
Chlorozotocin	ANLL	Therapeutic agent	Direct-acting bifunctional alkylating agent.	Mutation resulting from DNA binding and/or chromosomal alterations		IARC, 1987b; Vogelet al., 1998
Adriamycin	ANLL	Therapeutic agent	Topoisomerase II-poison and redox-cycling agent	Mutation resulting from chromosomal breakage and translocations		IARC, 1987b
Teniposide	ANLL	Therapeutic agent	Topoisomerase II-poison	Mutation resulting from chromosomal breakage and translocations		IARC, 2000c
Azacytidine	Leukemia	Therapeutic agent	DNA-methyltransferase inhibitor through metabolism and incorporation into DNA.	Alters DNA methylation and gene expression. Is also genotoxic.		NTP, 2005; Stresemann and Lyko, 2008
Chloramphenicol	ANLL	Therapeutic agent	Binds to ribosomal subunit blocking protein synthesis in mitochondria. Metabolite may also induce DNA damage	Unknown, presumed to be mutation resulting from DNA damage and/or chromosomal alterations		NTP, 2005

[a]Limited Evidence

Table 9. General characteristics of human leukemias and related neoplasms induced by recognized leukemia-inducing agents

Agent	Disease[a]	FAB[a]	MDS[b]	Typical clonal Chromosome Abnormalities	Latency (yrs)[c]
Ionizing radiation	AML ALL CML	M1−M6 L1−L2	+++	−7, −5, 7q−, 5q− t(9;22)	5−7 8 5
Alkylating agent chemotherapeutic drugs	AML	M1, M2	+++	−7, −5, 7q−, 5q−	~5
Ethylene oxide	{CLL}[d] {NHL} {MM}	?	-	?	?
1,3-Butadiene	{CLL} {CML} {NHL}	?	-	?	?
Epipodophyllotoxin topoisomerase II inhibitors	AML	M4, M5	+/−	t(11q23)	2−3
Dioxopiperazine topoisomerase II inhibitors	AML	M2, M3	+/−	t(8;21) t(15;17)	3
Benzene	AML {ALL} {CLL} {NHL} {MM}	M1, M2, M6 M3	++	Mixed[e] t(8;21), t(15;17)	<12
Formaldehyde	AML {CML}	?	-	?	?

[a]See Figure 3, for abbreviations on the types of lymphohematopoietic neoplasms and the leukemia subtypes classified according to the French-American-British (FAB) system.
[b]MDS = myelodysplastic syndrome.
[c]Approximate median latency period.
[d]Neoplasms in brackets indicate that there is limited evidence that they are induced by the agent.
[e]Clonal chromosomal abnormalities are present, but the karyotypes reported to date have been inconsistent. Two recent reports have provided additional evidence for the involvement of t(8;21) and t(15;17) (Mondrala and Eastmond, 2009; Wonget al., 2010).

Adapted from Eastmond (1997) and Eastmond et al. (2005) and reprinted by permission from Elsevier.

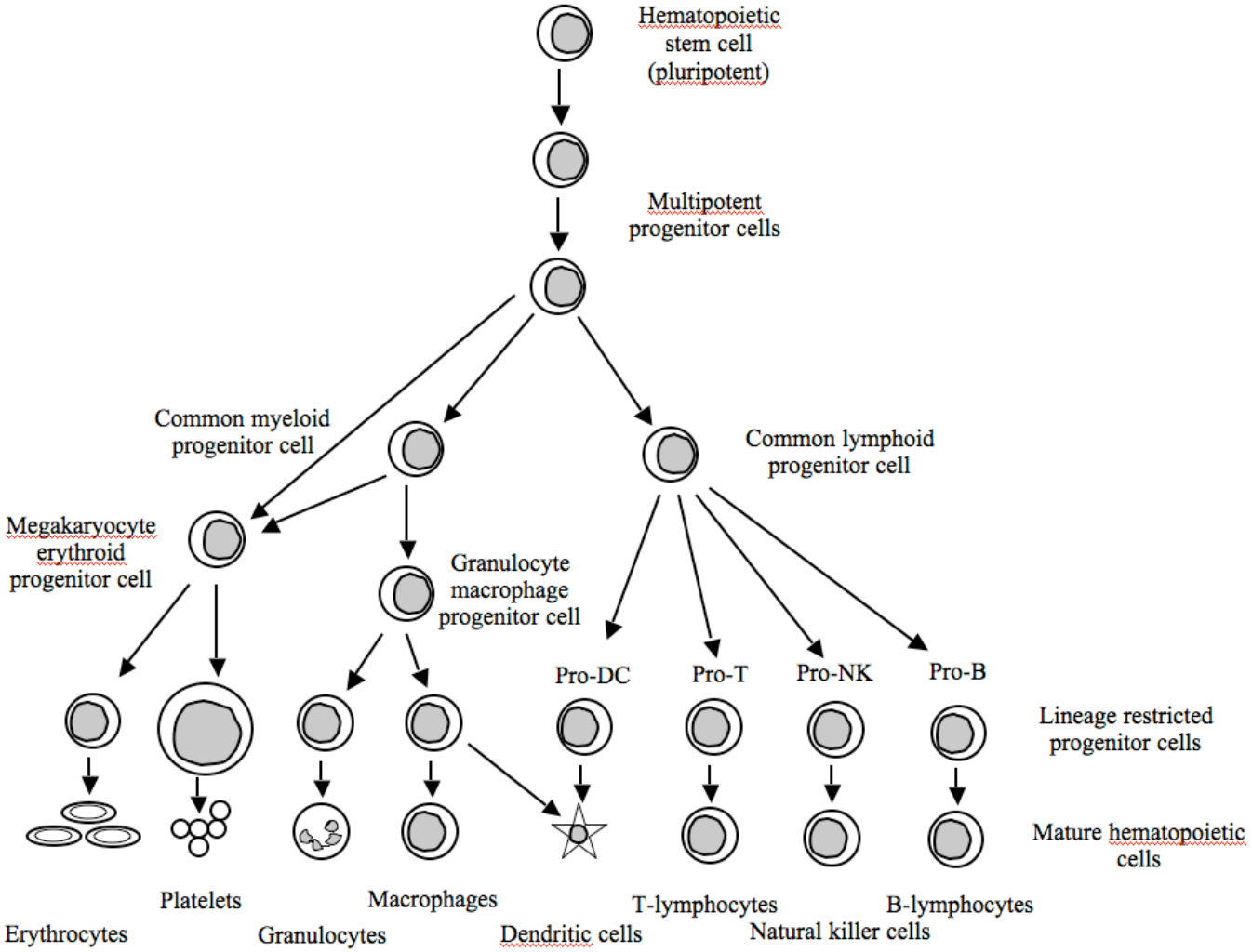

Figure 1. Simplified model of hematopoiesis showing lineages of major types of hematopoietic cells.

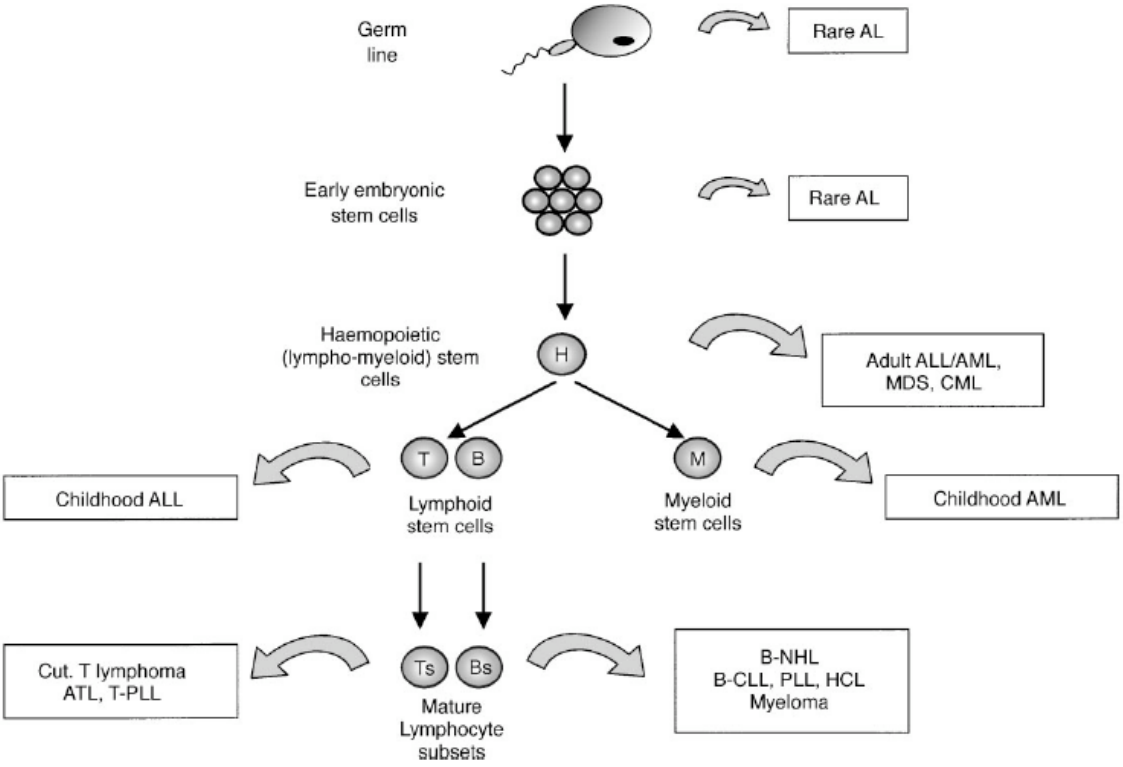

Figure 2. Hierarchical stem cell origins of leukemia and related cancers. The arrows denote the likely level of clonal selection for the majority of the leukemia subtypes listed.

Abbreviations: AL = acute leukemia; Cut. T lymphoma = cutaneous T-cell lymphoma; ATL = adult T-cell leukemia; T-PLL = T-cell prolymphocytic leukemia; B-cell non-Hodgkin lymphoma; PLL = prolymphocytic leukemia; HCL = hairy cell leukemia. For other abbreviations, see Table 1.

Source: Greaves (1999). Reprinted by permission from Elsevier.

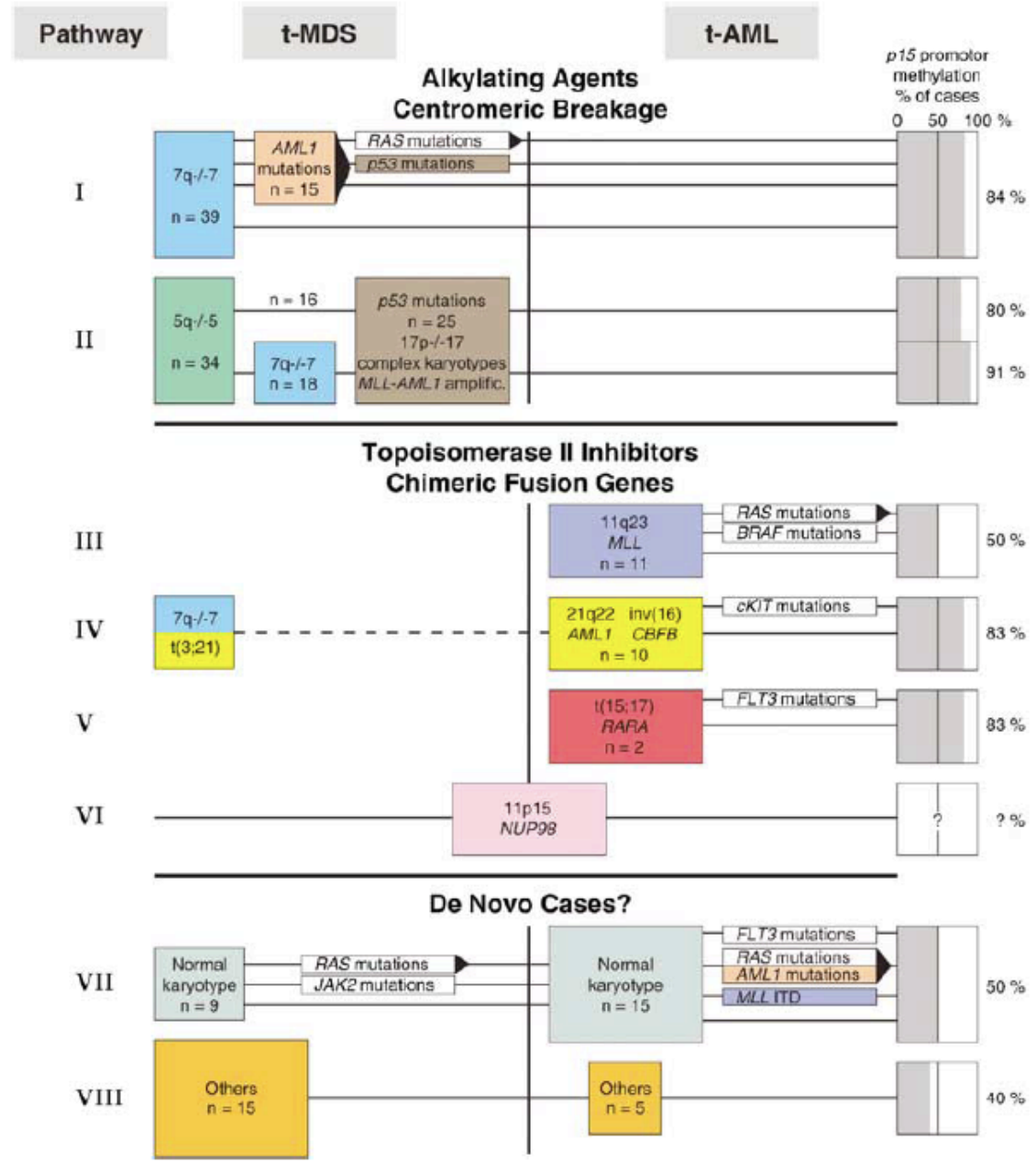

Figure 3. Genetic pathways of t-MDS and t-AML based on 140 cases from the Copenhagen study group. The black triangle indicates significant association with transformations from t-MDS to t-AML.

Source: Pedersen-Bjergaardet al. (2006). Reprinted by permission from Macmillan Publishers Ltd.

REFERENCES

ACS (American Cancer Society). (2006) Cancer facts & figures 2006. Atlanta, GA: American Cancer Society. Available online at http://www.cancer.org/downloads/STT/CAFF2006PWSecured.pdf.

ACS (American Cancer Society). (2009) Cancer facts & figures 2009. Atlanta, GA: American Cancer Society. Available online at http://www.cancer.org/downloads/STT/500809web.pdf.

Aksoy, M. (1988) Benzene hematoxicity. In: Aksoy, M; ed. Benzene carcinogenicity. Boca Raton, FL: CRC Press; pp. 113−144.

Aksoy, M; Erdem, S; DinCol, G. (1974) Leukemia in shoe-workers exposed chronically to benzene. Blood 44(6):837−841.

Aksoy, M; Erdem, S; Dincol, G; et al. (1984) Aplastic anemia due to chemicals and drugs: a study of 108 patients. Sex Transm Dis 11(4 Suppl):347−350.

Amiel, A; Yukla, M; Yogev, S; et al. (2004) Deletion of 5q31 and 7q31 in patients with stable melphalan treated multiple myeloma. Cancer Genet Cytogenet 152:84−87.

Andersen, MK; Johansson, B; Larsen, SO; et al. (1998) Chromosomal abnormalities in secondary MDS and AML. Relationship to drugs and radiation with specific emphasis on the balanced rearrangements. Haematologica 83(6):483−488.

Andersen, MK; Christiansen, DH; Jensen, BA; et al. (2001) Therapy-related acute lymphoblastic leukaemia with MLL rearrangements following DNA topoisomerase II inhibitors, an increasing problem: report on two new cases and review of the literature since 1992. Br J Haematol 114(3):539−543.

Anderson, RD; Berger, NA. (1994) Mutagenicity and carcinogenicity of topoisomerase-interactive agents. Mutat Res 309:109−142.

Aplan, PD. (2006) Chromosomal translocations involving the MLL gene: molecular mechanisms. DNA Repair (Amst) 5(9−10):1265−1272.

Asou, H; Matsui, H; Ozaki, Y; et al. (2009) Identification of a common microdeletion cluster in 7q21.3 subband among patients with myeloid leukemia and myelodysplastic syndrome. Biochem Biophys Res Commun 383(2):245−251.

Baan, R; Grosse, Y; Straif, K; et al. (2009) A review of human carcinogens--Part F: chemical agents and related occupations. Lancet Oncol 10(12):1143−1144.

Bagby, GCJ. (1994) Hematopoiesis. In: Stamatoyannopoulos, G; Nienhuis, AW; Majerus, PW; et al.; eds.The molecular basis of blood diseases. Philadelphia, PA: W.B. Saunders Company; pp. 71−103.

Basecke, J; Karim, K; Podleschny, M; et al. (2006) MLL rearrangements emerge during spontaneous apoptosis of clinical blood samples. Leukemia 20(6):1193−1194.

Basecke J; Podleschny M; Becker A; et al. (2008) Therapy-associated genetic aberrations in patients treated for non-Hodgkin lymphoma. Br J Haematol. 141(1):52-9.

Beane Freeman, LE; Blair, A; Lubin, JH; et al. (2009) Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. J Natl Cancer Inst 101(10):751−761.

Betti, CJ; Villalobos, MJ; Jiang, Q; et al. (2005) Cleavage of the MLL gene by activators of apoptosis is independent of topoisomerase II activity. Leukemia 19(12):2289−2295.

Bhatia, S; Ross, JA; Greaves, MF; et al. (1999) Epidemiology and etiology. In: Pui, C-H; ed. Childhood leukemias. New York, NY: Cambridge University Press; pp. 38−49.

Blanco, JG; Edick, MJ; Hancock, ML; et al. (2002) Genetic polymorphisms in CYP3A5, CYP3A4 and NQO1 in children who developed therapy-related myeloid malignancies. Pharmacogenetics 12(8):605−611.

Blatt, J. (1995) Second malignancies associated with doxorubicin [editorial., comment]. Pediatr Hematol Oncol 12(2):111−113.

Bo, J; Schroder, H; Kristinsson, J; et al. (1999) Possible carcinogenic effect of 6-mercaptopurine on bone marrow stem cells: relation to thiopurine metabolism. Cancer 86(6):1080−1086.

Boffetta, P; Kaldor, JM. (1994) Secondary malignancies following cancer chemotherapy. Acta Oncol 33(6):591−598.

Boffetta, P; van der Hel, O; Norppa, H; et al. (2007) Chromosomal aberrations and cancer risk: results of a cohort study from Central Europe. Am J Epidemiol 165:36−43.

Boice, J, Jr; Blettner, M; Kleinerman, RA; et al. (1987) Radiation dose and leukemia risk in patients treated for cancer of the cervix. J Natl Cancer Inst 79(6):1295−1311.

Bouvard, V; Baan, R; Straif, K; et al. (2009) A review of human carcinogens--Part B: biological agents. Lancet Oncol 10(4):321−322.

Bowen, DT; Frew, ME; Hills, R; et al. (2005) RAS mutation in acute myeloid leukemia is associated with distinct cytogenetic subgroups but does not influence outcome in patients younger than 60 years. Blood 106(6):2113−2119.

Bryder, D; Rossi, DJ; Weissman, IL. (2006) Hematopoietic stem cells: the paradigmatic tissue-specific stem cell. Am J Pathol 169(2):338−346.

Byrne, JL; Marshall, CJ. (1998) The molecular pathophysiology of myeloid leukaemias: Ras revisited. Br J Haematol 100(2):256−264.

Cadman, EC; Capizzi, RL; Bertino, JR. (1977) Acute nonlymphocytic leukemia: a delayed complication of Hodgkin's disease therapy: analysis of 109 cases. Cancer 40(3):1280−1296.

Canaani, E; Nowell, PC; Croce, CM. (1995) Molecular genetics of 11q23 chromosome translocations. Adv Cancer Res 66:213−234.

Casciato, DA; Scott, JL. (1979) Acute leukemia following prolonged cytotoxic agent therapy. Medicine (Baltimore) 58:32−47.

Castro, PD; Liang, JC; Nagarajan, L. (2000) Deletions of chromosome 5q13.3 and 17p loci cooperate in myeloid neoplasms. Blood 95(6):2138−2143.

Chen, Z; Sandberg, AA. (2002) Molecular cytogenetic aspects of hematological malignancies: clinical implications. Am J Med Genet 115(3):130−141.

Cheok, MH; Evans, WE. (2006) Acute lymphoblastic leukaemia: a model for the pharmacogenomics of cancer therapy. Nat Rev Cancer 6(2):117−129.

Cheok, MH; Lugthart, S; Evans, WE. (2006) Pharmacogenomics of acute leukemia. Annu Rev Pharmacol Toxicol 46:317−353.

Choi KE; Ratain MJ; Williams SF; et al. (1989) Plasma pharmacokinetics of high-dose oral melphalan in patients treated with trialkylator chemotherapy and autologous bone marrow reinfusion. Cancer Res. 49(5):1318-21.

Christiansen, DH; Andersen, MK; Pedersen-Bjergaard, J. (2001) Mutations with loss of heterozygosity of p53 are common in therapy-related myelodysplasia and acute myeloid leukemia after exposure to alkylating agents and significantly associated with deletion or loss of 5q, a complex karyotype, and a poor prognosis. J Clin Oncol 19(5):1405−1413.

Christiansen, DH; Andersen, MK; Pedersen-Bjergaard, J. (2004) Mutations of AML1 are common in therapy-related myelodysplasia following therapy with alkylating agents and are significantly associated with deletion or loss of chromosome arm 7q and with subsequent leukemic transformation. Blood 104(5):1474−1481.

Christiansen, DH; Andersen, MK; Desta, F; et al. (2005) Mutations of genes in the receptor tyrosine kinase (RTK)/RAS-BRAF signal transduction pathway in therapy-related myelodysplasia and acute myeloid leukemia. Leukemia 19(12):2232−2240.

Cochrane, JE; Skopek, TR. (1993) Mutagenicity of 1,3-butadiene and its epoxide metabolites in human TK6 cells and in splenic T cells isolated from exposed B6C3F1 mice. IARC Sci Publ 127:195−204.

Cochrane, JE; Skopek, TR. (1994) Mutagenicity of butadiene and its epoxide metabolites: II. Mutational spectra of butadiene, 1,2-epoxybutene and diepoxybutane at the hprt locus in splenic T cells from exposed B6C3F1 mice. Carcinogenesis 15(4):719−723.

Corral, J; Lavenir, I; Impey, H; et al. (1996) An Mll-AF9 fusion gene made by homologous recombination causes acute leukemia in chimeric mice: a method to create fusion oncogenes. Cell 85(6):853−861.

Cozzio, A; Passegue, E; Ayton, PM; et al. (2003) Similar MLL-associated leukemias arising from self-renewing stem cells and short-lived myeloid progenitors. Genes Dev 17(24):3029−3035.

Cullings, HM; Fujita, S; Funamoto, S; et al. (2006) Dose estimation for atomic bomb survivor studies: its evolution and present status. Radiat Res 166(1 Pt 2):219−254.

Curtis, RE; Boice, JD, Jr; Stovall, M; et al. (1994) Relationship of leukemia risk to radiation dose following cancer of the uterine corpus. J Natl Cancer Inst 86(17):1315−1324.

Davies, SM. (2000) Therapy-related leukemia: is the risk life-long and can we identify patients at greatest risk. J Pediatr Hematol Oncol 22(4):302−305.

Deguchi, K; Gilliland, DG. (2002) Cooperativity between mutations in tyrosine kinases and in hematopoietic transcription factors in AML. Leukemia 16(4):740−744.

Deschler, B; Lubbert, M. (2006) Acute myeloid leukemia: epidemiology and etiology. Cancer 107(9):2099−2107.

Dobson, CL; Warren, AJ; Pannell, R; et al. (1999) The mll-AF9 gene fusion in mice controls myeloproliferation and specifies acute myeloid leukaemogenesis. Embo J 18(13):3564−3574.

Donner, EM; Wong, BA; James, RA; et al. (2010) Reciprocal translocations in somatic and germ cells of mice chronically exposed by inhalation to ethylene oxide: implications for risk assessment. Mutagenesis 25:49−55.

Downing, JR. (1999) Molecular genetics of acute myeloid leukemia. In: Pui, C-H, ed. Childhood leukemias. New York, NY: Cambridge University Press; pp. 219−254.

Dzierzak, E; Speck, NA. (2008) Of lineage and legacy: the development of mammalian hematopoietic stem cells. Nat Immunol 9(2):129−136.

Eastmond, DA. (1997) Chemical and radiation leukemogenesis in humans and rodents and the value of rodent models for assessing risks of lymphohematopoietic cancers. Environmental Protection Agency, Washington DC; EPA/600/R-97/090. Avaliable online at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12181.

Eastmond, DA; Mondrala, ST; Hasegawa, L. (2005) Topoisomerase II inhibition by myeloperoxidase-activated hydroquinone: a potential mechanism underlying the genotoxic and carcinogenic effects of benzene. Chem Biol Interact 153−154:207−216.

Ebert, BL. (2009) Deletion 5q in myelodysplastic syndrome: a paradigm for the study of hemizygous deletions in cancer. Leukemia 23(7):1252−1256.

Eguchi-Ishimae, M; Eguchi, M; Ishii, E; et al. (2001) Breakage and fusion of the TEL (ETV6) gene in immature B lymphocytes induced by apoptogenic signals. Blood 97(3):737−743.

Eguchi-Ishimae, M; Eguchi, M; Ishii, E; et al. (2005) The association of a distinctive allele of NAD(P)H:quinone oxidoreductase with pediatric acute lymphoblastic leukemias with MLL fusion genes in Japan. Haematologica 90(11):1511−1515.

El Ghissassi, F; Baan, R; Straif, K; et al. (2009) A review of human carcinogens--part D: radiation. Lancet Oncol 10(8):751−752.

Ember, I; Kiss, I; Gombkoto, G; et al. (1998a) Oncogene and suppressor gene expression as a biomarker for ethylene oxide exposure. Cancer Detect Prev 22(3):241−245.

Ember, I; Kiss, I; Malovics, I. (1998b) Oncogene and tumour suppressor gene expression changes in persons exposed to ethylene oxide. Eur J Cancer Prev 7(2):167−168.

Felix, CA. (1998) Secondary leukemias induced by topoisomerase-targeted drugs. Biochim Biophys Acta 1400(1−3):233−255.

Felix, CA; Kolaris, CP; Osheroff, N. (2006) Topoisomerase II and the etiology of chromosomal translocations. DNA Repair (Amst) 5(9−10):1093−1108.

Ferguson, LR; Pearson, AE. (1996) The clinical use of mutagenic anticancer drugs. Mutat Res 355(1−2):1−12.

Forster, A; Pannell, R; Drynan, LF; et al. (2003) Engineering de novo reciprocal chromosomal translocations associated with Mll to replicate primary events of human cancer. Cancer Cell 3(5):449−458.

Gadner, H; Masera, G; Schrappe, M; et al. (2006) The eighth international childhood acute lymphoblastic leukemia workshop ('Ponte di legno meeting') report: Vienna, Austria, April 27−28, 2005. Leukemia 20:9−17.

Gale, RP. (1988) Myelosuppressive effects of antineoplastic chemotherapy. In: Testa, NG; Gale, RP; eds. Hematopoiesis: long-term effects of chemotherapy and radiation. New York, NY: Marcel Dekker; pp. 63−73.

Gibbons, B; Lillington, DM; Monard, S; et al. (1994) Fluorescence in situ hybridisation studies to characterise complete and partial monosomy 7 in myeloid disorders. Genes Chromosomes Cancer 10(4):244−249.

GlaxoSmithKline. (2007) Alkeran (melphalan) tablets; Prescribing information provided by the GlaxoSmithKine available at: us.gsk.com/products/assets/us_**alkeran**_tablets.pdf. p. 8.

Gocke, E; Muller, L. (2009) In vivo studies in the mouse to define a threshold for the genotoxicity of EMS and ENU. Mutat Res 678(2):101−107.

Gocke, E; Ballantyne, M; Whitwell, J; et al. (2009) MNT and MutaMouse studies to define the in vivo dose response relations of the genotoxicity of EMS and ENU. Toxicol Lett 190(3):286−297.

Goldfrank, LR; Flomenbaum, NE; Newin, NA; et al. (2002) Goldfrank's toxicologic emergencies. New York, NY: McGraw-Hill Professional.

Greaves, M. (1999) Molecular genetics, natural history and the demise of childhood leukaemia. Eur J Cancer 35(14):1941−1953.

Greaves, MF; Wiemels, J. (2003) Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer 3(9):639−649.

Grosse, Y; Baan, R; Straif, K; et al. (2009) A review of human carcinogens-Part A: pharmaceuticals. Lancet Oncol 10:13−14.

Guillem, V; Tormo, M. (2008) Influence of DNA damage and repair upon the risk of treatment related leukemia. Leuk Lymphoma 49(2):204−217.

Gundestrup, M; Andersen, MK; Sveinbjornsdottir, E; et al. (2000) Cytogenetics of myelodysplasia and acute myeloid leukaemia in aircrew and people treated with radiotherapy. Lancet 356(9248):2158.

Haferlach, T; Kern, W; Schnittger, S; Schoch, C. (2005) Modern diagnostics in acute leukemias. Crit Rev Oncol Hematol 56(2):223−234.

Hagmar, L; Bonassi, S; Stromberg, U; et al. (1998) Chromosomal aberrations in lymphocytes predict human cancer: a report from the European Study Group on Cytogenetic Biomarkers and Health (ESCH). Cancer Res 58(18):4117−4121.

Hagmar, L; Stromberg, U; Bonassi, S; et al. (2004) Impact of types of lymphocyte chromosomal aberrations on human cancer risk: results from Nordic and Italian cohorts. Cancer Res 64(6):2258−2263.

Harada, H; Harada, Y; Tanaka, H; et al. (2003) Implications of somatic mutations in the AML1 gene in radiation-associated and therapy-related myelodysplastic syndrome/acute myeloid leukemia. Blood 101(2):673−680.

Harris, NL; Stein, H; Coupland, SE; et al. (2001) New approaches to lymphoma diagnosis. Hematology Am Soc Hematol Educ Program 2001:194−220.

Hartley, JA; O'Hare, CC; Baumgart, J. (1999) DNA alkylation and interstrand cross-linking by treosulfan. Br J Cancer 79(2):264−266.

Hasle, H; Niemeyer, CM; Chessells, JM; et al. (2003) A pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases. Leukemia 17(2):277−282.

Haupt, R; Comelli, A; Rosanda, C; et al. (1993) Acute myeloid leukemia after single-agent treatment with etoposide for Langerhans' cell histiocytosis of bone. Am J Pediatr Hematol Oncol 15(2):255−257.

Hauptmann, M; Lubin, JH; Stewart, PA; et al. (2003) Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. J Natl Cancer Inst 95(21):1615−1623.

Head, DR; Pui, C-H. (1999) Diagnosis and classification. In: Pui, C-H; ed. Childhood leukemias. Cambridge, UK: Cambridge University Press; pp. 19−37.

Hendry, JH; Feng-Tong, Y. (1995) Response of bone marrow to low LET irradiation. In: Hendry, JH; Lord, BI; eds. Radiation toxicology: bone marrow and leukemia. London: Taylor & Francis; pp. 91−116.

Herry, A; Douet-Guilbert, N; Morel, F; et al. (2007) Redefining monosomy 5 by molecular cytogenetics in 23 patients with MDS/AML. Eur J Haematol 78(6):457−467.

Hijiya, N; Ness, KK; Ribeiro, RC; et al. (2009) Acute leukemia as a secondary malignancy in children and adolescents: current findings and issues. Cancer 115:23−35.

Hjalgrim, H; Engels, EA. (2008) Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence. J Intern Med 264(6):537−548.

Hodgson, DC; Gilbert, ES; Dores, GM; et al. (2007) Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. J Clin Oncol 25(12):1489−1497.

Holsapple, MP; Karras, JG; Ledbetter, JA; et al. (1996) Molecular mechanisms of toxicant-induced immunosuppression: role of second messengers. Annu Rev Pharmacol Toxicol 36:131−159.

Hong, HH; Houle, CD; Ton, TV; et al. (2007) K-ras mutations in lung tumors and tumors from other organs are consistent with a common mechanism of ethylene oxide tumorigenesis in the B6C3F1 mouse. Toxicol Pathol 35:81−85.

Hosgood, HD; III, Zhang, L; Shen, M; et al. (2009) Association between genetic variants in VEGF, ERCC3 and occupational benzene haematotoxicity. Occup Environ Med 66(12):848−853.

Houle, CD; Ton, TV; Clayton, N; et al. (2006) Frequent p53 and H-ras mutations in benzene- and ethylene oxide-induced mammary gland carcinomas from B6C3F1 mice. Toxicol Pathol 34(6):752−762.

Hrusak, O; Trka, J; Zuna, J; et al. (2002) Acute lymphoblastic leukemia incidence during socioeconomic transition: selective increase in children from 1 to 4 years. Leukemia 16(4):720−725.

Hunger, SP; Sklar, J; Link, MP. (1992) Acute lymphoblastic leukemia occurring as a second malignant neoplasm in childhood: report of three cases and review of the literature. J Clin Oncol 10:156−163.

IARC (International Agency for Research on Cancer). (1987a) IARC monographs on the evaluation of carcinogenic risks to humans. Suppl. 6. Genetic and related effects: an updating of selected IARC monographs from volumes 1 to 42. Lyon, France: International Agency for Research on Cancer.

IARC (International Agency for Research on Cancer). (1987b) IARC monographs on the evaluation of carcinogenic risks to humans. Suppl. 7. Overall evaluations of carcinogenicity: an updating of selected IARC monographs from volumes 1 to 42. Lyon, France: International Agency for Research on Cancer. Available online at http://monographs.iarc.fr/ENG/Monographs/suppl7/suppl7.pdf

IARC (International Agency for Research on Cancer). (1990a) Azacitidine. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 50. Pharmaceutical Drugs. Lyon, France: International Agency for Research on Cancer; pp 47−64. Available online at http://monographs.iarc.fr/ENG/Monographs/vol50/mono50-6.pdf

IARC (International Agency for Research on Cancer). (1990b) Chlorozotocin. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 50. Pharmaceutical Drugs. Lyon, France: International Agency for Research on Cancer; pp 65−76. Available online at http://monographs.iarc.fr/ENG/Monographs/vol50/mono50-7.pdf

IARC (International Agency for Research on Cancer). (1990c) Ciclosporin. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 50. Pharmaceutical Drugs. Lyon, France: International Agency for Research on Cancer; .pp 77−114. Available online at http://monographs.iarc.fr/ENG/Monographs/vol50/mono50-8.pdf

IARC (International Agency for Research on Cancer). (1994) Ethylene oxide. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 60. Some industrial chemicals. Lyon, France: International Agency for Research on Cancer; pp 73−160. Available online at http://monographs.iarc.fr/ENG/Monographs/vol60/mono60-7.pdf.

IARC (International Agency for Research on Cancer). (1996a) Human immunodeficiency viruses. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 67. Human immunodeficiency viruses and human T-cell lymphotropic viruses. Lyon, France: International Agency for Research on Cancer. Pp 31−260. Available online at http://monographs.iarc.fr/ENG/Monographs/vol67/mono67-5.pdf.

IARC (International Agency for Research on Cancer). (1996b) Human T-cell lymphotrophic viruses. Vol 67. Human immunodeficiency viruses and human T-cell lymphotropic viruses.Lyon, France: International Agency for Research on Cancer. Pp 261−390. Available online at http://monographs.iarc.fr/ENG/Monographs/vol67/mono67-6.pdf.

IARC (International Agency for Research on Cancer). (1997) Epstein−Barr virus. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 70. Epstein-Barr virus and Kaposi's sarcoma herpesvirus/human herpesvirus 8.Lyon, France: International Agency for Research on Cancer, Lyon; pp 47−374. Available online at http://monographs.iarc.fr/ENG/Monographs/vol70/mono70-7.pdf.

IARC (International Agency for Research on Cancer). (1999) 1,3-Butadiene. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 71. Re-evaluation of some organic chemicals, hydrazine and hydrogenperoxide. Lyon, France: International Agency for Research on Cancer; pp 109−226. Available online at http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-8.pdf.

IARC (International Agency for Research on Cancer). (2000a) Etoposide. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 76. Some antiviral and antineoplastic drugs, and other pharmaceutical agents. Lyon, France: International Agency for Research on Cancer; pp. 175−257. Available online at http://monographs.iarc.fr/ENG/Monographs/vol76/mono76-10.pdf.

IARC (International Agency for Research on Cancer). (2000b) IARC monographs on the evaluation of carcinogenic risks to humans. Vol 75. Ionizing radiation, part 1: X- and gamma (γ)-radiation, and neutrons. Lyon, France: International Agency for Research on Cancer. Available online at http://monographs.iarc.fr/ENG/Monographs/vol75/mono75.pdf.

IARC (International Agency for Research on Cancer). (2000c) Teniposide. IARC monographs on the evaluation of carcinogenic risks to humans.Vol 76. Lyon, France: International Agency for Research on Cancer; 259−287. Available online at http://monographs.iarc.fr/ENG/Monographs/vol76/mono76-11.pdf.

IARC (International Agency for Research on Cancer). (2001) IARC monographs on the evaluation of carcinogenic risks to humans. Vol 78. Ionizing radiation, part 2: some internally deposited radionuclides. Lyon, France: International Agency for Research on Cancer. Available onine at http://monographs.iarc.fr/ENG/Monographs/vol78/mono78.pdf.

IARC (International Agency for Research on Cancer). (2004) IARC monographs on the evaluation of carcinogenic risks to humans. Vol 83. Tobacco smoke and involuntary smoking. Lyon, France: International Agency for Research on Cancer. Available online at http://monographs.iarc.fr/ENG/Monographs/vol83/mono83.pdf.

IARC (International Agency for Research on Cancer). (2006) Formaldehyde. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 88.Formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. Lyon,

France: International Agency for Research on Cancer;.pp 37−326. Available online at http://monographs.iarc.fr/ENG/Monographs/vol88/mono88-6.pdf.

IARC (International Agency for Research on Cancer). (2008a) 1,3-Butadiene. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 97. 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). Lyon, France: International Agency for Research on Cancer; pp.45−184. Available online at http://monographs.iarc.fr/ENG/Monographs/vol97/mono97-6.pdf.

IARC (International Agency for Research on Cancer). (2008b) Ethylene oxide. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 97. 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). Lyon, France: International Agency for Research on Cancer. pp 185−309.

IARC (International Agency for Research on Cancer). (2008c) General remarks. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 97. 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). Lyon, France: International Agency for Research on Cancer; pp 39−41. Available online at http://monographs.iarc.fr/ENG/Monographs/vol97/mono97-5.pdf.

IARC (International Agency for Research on Cancer). (2008d) Preamble. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 97. 1,3-butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). Lyon, France: International Agency for Research on Cancer; pp 9−38. Available online at http://monographs.iarc.fr/ENG/Monographs/vol97/mono97-4.pdf.

IARC (International Agency for Research on Cancer). (2009) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 100. A review of human carcinogens - Part F: Chemical agents and related occupations. Lyon, France: International Agency for Research on Cancer; pp. 33. Available online at http://monographs.iarc.fr/pdfnews/WG-100F.pdf.

IARC (International Agency for Research on Cancer). (2010) Overall evaluations of carcinogenicity to humans. Lyon, France: International Agency for Research on Cancer.

Imashuku, S; Hibi, S; Bessho, F; et al. (2003) Detection of myelodysplastic syndrome/ acute myeloid leukemia evolving from aplastic anemia in children, treated with recombinant human G-CSF. Haematologica 88(11):ECR31.

Irons, RD; Lv, L; Gross, SA; et al. (2005) Chronic exposure to benzene results in a unique form of dysplasia. Leuk Res 29(12):1371−1380.

Iwasaki, H; Akashi, K. (2007) Hematopoietic developmental pathways: on cellular basis. Oncogene 26(47):6687−6696.

Jaiswal, S; Weissman, IL. (2009) Hematopoietic stem and progenitor cells and the inflammatory response. Ann N Y Acad Sci 1174:118−121.

Jandl, JH. (1987) Blood: Textbook of Hematology. Boston, MA: Little, Brown and Company.

Jandl, JH. (1996) Blood: Textbook of Hematology. Boston, MA: Little, Brown and Company.

Jansen, JG; Vrieling, H; van Teijlingen, CM; et al. (1995) Marked differences in the role of O6-alkylguanine in hprt mutagenesis in T-lymphocytes of rats exposed in vivo to ethylmethanesulfonate, N-(2-hydroxyethyl)-N-nitrosourea, or N-ethyl-N-nitrosourea. Cancer Res 55(9):1875−1882.

Kaldor, JM; Day, NE; Pettersson, F; et al. (1990) Leukemia following chemotherapy for ovarian cancer. N Engl J Med 322:1−6.

Kamada, N; Tanaka, K. (1983) Cytogenetic studies of hematological disorders in atomic bomb survivors. In: Ishihara, T; Sasaki, MS; eds. Radiation-induced chromosome damage in man. New York, NY: Alan R. Liss; pp. 455−474.

Kantarjian, HM; Keating, MJ. (1987) Therapy-related leukemia and myelodysplastic syndrome. Cancer 40(4):435−443.

Karran, P. (2006) Thiopurines, DNA damage, DNA repair and therapy-related cancer. Br Med Bull 79−80:153−170.

Karran, P; Offman, J; Bignami, M. (2003) Human mismatch repair, drug-induced DNA damage, and secondary cancer. Biochimie 85(11):1149−1160.

Kelly, LM; Gilliland, DG. (2002) Genetics of myeloid leukemias. Annu Rev Genomics Hum Genet 3:179−198.

Kim, YJ; Choi, JY; Paek, D; et al. (2008) Association of the NQO1, MPO, and XRCC1 polymorphisms and chromosome damage among workers at a petroleum refinery. J Toxicol Environ Health A 71(5):333−341.

Klymenko, S; Trott, K; Atkinson, M; et al. (2005) Aml1 gene rearrangements and mutations in radiation-associated acute myeloid leukemia and myelodysplastic syndromes. J Radiat Res (Tokyo) 46(2):249−255.

Krestinina, L; Preston, DL; Davis, FG; et al. (2010) Leukemia incidence among people exposed to chronic radiation from the contaminated Techa River, 1953−2005. Radiat Environ Biophys. Doi 10.1007/s00411-009-0257-5 (In Press)

Lan, Q; Zhang, L; Li, G; et al. (2004) Hematotoxicity in workers exposed to low levels of benzene. Science 306(5702):1774−1776.

Larson, RA; Wang, Y; Banerjee, M; et al. (1999) Prevalence of the inactivating 609C-->T polymorphism in the NAD(P)H:quinone oxidoreductase (NQO1) gene in patients with primary and therapy-related myeloid leukemia. Blood 94(2):803−807.

Lavau, C; Luo, RT; Du, C; et al. (2000) Retrovirus-mediated gene transfer of MLL-ELL transforms primary myeloid progenitors and causes acute myeloid leukemias in mice. Proc Natl Acad Sci U S A 97(20):10984−10989.

Lawley, PD; Phillips, DH. (1996) DNA adducts from chemotherapeutic agents. Mutat Res 355(1−2):13−40.

Le Deley, MC; Leblanc, T; Shamsaldin, A; et al. (2003) Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Societe Francaise d'Oncologie Pediatrique. J Clin Oncol 21(6):1074−1081.

Le, H; Singh, S; Shih, SJ; et al. (2009) Rearrangements of the MLL gene are influenced by DNA secondary structure, potentially mediated by topoisomerase II binding. Genes Chromosomes Cancer 48(9):806−815.

Leone, G; Mele, L; Pulsoni, A; et al. (1999) The incidence of secondary leukemias. Haematologica 84(10):937−945.

Leone, G; Voso, MT; Sica, S; et al. (2001) Therapy related leukemias: susceptibility, prevention and treatment. Leuk Lymphoma 41(3−4):255−276.

Leone, G; Pagano, L; Ben-Yehuda, D; et al. (2007) Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica 92(10):1389−1398.

Leone, G; Fianchi, L; Pagano, L; et al. (2010) Incidence and susceptibility to therapy-related myeloid neoplasms. Chem Biol Interact 184(1-2):39−45.

Levesque, JP; Winkler, IG; Larsen, SR; et al. (2007) Mobilization of bone marrow-derived progenitors. Handb Exp Pharmacol 180:3−36.

Levine, EG; Bloomfield, CD. (1992) Leukemias and myelodysplastic syndromes secondary to drug, radiation, and environmental exposure. Semin Oncol 19:47−84.

Li, Z; and Li, L. (2006) Understanding hematopoietic stem-cell microenvironments. Trends Biochem Sci 31(10):589−595.

Liou, SH; Lung, JC; Chen, YH; et al. (1999) Increased chromosome-type chromosome aberration frequencies as biomarkers of cancer risk in a blackfoot endemic area. Cancer Res 59(7):1481−1484.

Loescher, LJ; Welch-McCaffrey, D; Leigh, SA; et al. (1989) Surviving adult cancers. Part 1: Physiologic effects [published erratum appears in Ann Intern Med 1990 Apr 15;112(8):634]. Ann Intern Med 111(5):411−432.

Lu, K; Collins, LB; Ru, H; et al. (2010) Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia. Toxicol Sci. 116(2):441-51.

Lutz, WK. (1990) Dose-response relationship and low dose extrapolation in chemical carcinogenesis. Carcinogenesis 11(8):1243−1247.

Lutz, WK. (2001) Susceptibility differences in chemical carcinogenesis linearize the dose-response relationship: threshold doses can be defined only for individuals. Mutat Res 482(1−2):71−76.

Maanen, MJ; Smeets, CJ; Beijnen, JH. (2000) Chemistry, pharmacology and pharmacokinetics of N,N',N" -triethylenethiophosphoramide (ThioTEPA). Cancer Treat Rev 26(4):257−268.

Malik, E; Cohen, SB; Sahar, D; et al. (2006) The frequencies of NAD(P)H quinone oxidoreductase (NQO1) variant allele in Israeli ethnic groups and the relationship of NQO1*2 to adult acute myeloid leukemia in Israeli patients. Haematologica 91(7):956−959.

Mamuris, Z; Gerbault-Seureau, M; Prieur, M; et al. (1989) Chromosomal aberrations in lymphocytes of patients treated with melphalan. Int J Cancer 43:80−86.

Mamuris, Z; Dumont, J; Dutrillaux, B; et al. (1990) Specific chromosomal mutagenesis observed in stimulated lymphocytes from patients with S-ANLL. Int J Cancer 46(4):563−568.

Maris, JM; Wiersma, SR; Mahgoub, N; et al. (1997) Monosomy 7 myelodysplastic syndrome and other second malignant neoplasms in children with neurofibromatosis type 1. Cancer 79(7):1438−1446.

Matsuo, T; Tomonaga, M; Bennett, JM; et al. (1988) Reclassification of leukemia among A-bomb survivors in Nagasaki using French-American-British (FAB) classification for acute leukemia. Jpn J Clin Oncol 18(2):91−96.

Mauritzson, N; Albin, M; Rylander, L; et al. (2002) Pooled analysis of clinical and cytogenetic features in treatment-related and de novo adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976−1993 and on 5098 unselected cases reported in the literature 1974−2001. Leukemia 16(12):2366−2378.

Mays, AN; Osheroff, N; Xiao, Y; et al. (2010) Evidence for direct involvement of epirubicin in the formation of chromosomal translocations in t(15;17) therapy-related acute promyelocytic leukemia. Blood 115(2):326−330.

Meyer, C; Schneider, B; Jakob, S; et al. (2006) The MLL recombinome of acute leukemias. Leukemia 20(5):777−784.

Mihich, E; Metcalf, D. (1995) Sixth Annual Pezcoller Symposium: normal and malignant hematopoiesis--new advances. Cancer Res 55(15):3462−3466.

Mistry, AR; Felix, CA; Whitmarsh, RJ; et al. (2005) DNA topoisomerase II in therapy-related acute promyelocytic leukemia. N Engl J Med 352(15):1529−1538.

Mondrala, S; Eastmond, DA. (2009) Topoisomerase II inhibition by the bioactivated benzene metabolite hydroquinone involves multiple mechanisms. Chem Biol Interact 184(1–2):259−268.

Mrozek, K; Heerema, NA; Bloomfield, CD. (2004) Cytogenetics in acute leukemia. Blood Rev 18(2):115−136.

Müller AM; Duque J; Shizuru JA; Lübbert M. (2008) Complementing mutations in core binding factor leukemias: from mouse models to clinical applications. Oncogene. 27(44):5759-73.

Muller, L; Gocke, E; Lave, T; et al. (2009) Ethyl methanesulfonate toxicity in Viracept--a comprehensive human risk assessment based on threshold data for genotoxicity. Toxicol Lett 190(3):317−329.

Neglia, JP; Friedman, DL; Yasui, Y; et al. (2001) Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 93(8):618−629.

Neri, M; Ugolini, D; Bonassi, S; et al. (2006) Children's exposure to environmental pollutants and biomarkers of genetic damage. II. Results of a comprehensive literature search and meta-analysis. Mutat Res 612:14−39.

Nervi, C; Fazi, F; Grignani, F. (2008) Oncoproteins, heterochromatin silencing and microRNAs: a new link for leukemogenesis. Epigenetics 3:1−4.

Niazi, GA; Fleming, AF. (1989) Blood dyscrasia in unoffical vendors of petrol and heavy oil and motor mechanics in Nigeria. Trop Doct 19(2):55−58.

Nitiss, JL. (2009) DNA topoisomerase II and its growing repertoire of biological functions. Nat Rev Cancer 9(5):327−337.

Nowell, PC. (1991) Origins of human leukemia: an overview. In: Brugge, J; Curran, T; Harlow, E; et al.; eds. Origins of human cancer. A comprehensive review. Cold Spring Harbor Laboratory Press.

NRC (National Research Council). (1990) Health effects of exposure to low levels of ionizing radiation. BEIR V. Committee on the Biological Effects of Ionizing Radiation (BEIR). Washington, DC: National Academy Press.

NRC (National Research Council). (2006) Health risks from exposure to low levels of ionizing radiation. BEIR VII. Committee on the Biological Effects of Ionizing Radiation (BEIR). Washington, DC: National Academy Press.

NTP (National Toxicology Program). (2005) The Report of Carcinogens. Program, NT; ed. National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services, Research Triangle Park, NC.

Ohara, A; Kojima, S; Hamajima, N; et al. (1997) Myelodysplastic syndrome and acute myelogenous leukemia as a late clonal complication in children with acquired aplastic anemia. Blood 90(3):1009−1013.

Osborne, MR; Lawley, PD; Crofton-Sleigh, C; et al. (1995) Products from alkylation of DNA in cells by melphalan: human soft tissue sarcoma cell line RD and Escherichia coli WP2. Chem Biol Interact 97(3):287−296.

Papayannopoulou, T; Scadden, DT. (2008) Stem-cell ecology and stem cells in motion. Blood 111(8):3923−3930.

Passegue, E; Jamieson, CH; Ailles, LE; et al. (2003) Normal and leukemic hematopoiesis: are leukemias a stem cell disorder or a reacquisition of stem cell characteristics? Proc Natl Acad Sci U S A 100(Suppl. 1):11842−11849.

Pedersen-Bjergaard, J; Philip, P. (1987) Cytogenetic characteristics of therapy-related acute nonlymphocytic leukaemia, preleukaemia, and acute myeloproliferative syndrome: correlation with clinical data for 61 consucutive cases. Brit J Haemat 66(2):199−207.

Pedersen-Bjergaard, J; Philip, P. (1991) Two different classes of therapy-related and de-novo acute myeloid leukemia? Cancer Genet Cytogenet 55:119−124.

Pedersen-Bjergaard, J; Rowley, JD. (1994) The balanced and the unbalanced chromosome aberrations of acute myeloid leukemia may develop in different ways and may contribute differently to malignant transformation. Blood 83(10):2780−2786.

Pedersen-Bjergaard, J; Specht, L; Larsen, SO; et al. (1987) Risk of therapy-related leukaemia and preleukaemia after Hodgkin's disease. Relation to age, cumulative dose of alkylating agents, and time from chemotherapy. Lancet 2(8550):83−88.

Pedersen-Bjergaard, J; Pedersen, M; Roulston, D; et al. (1995) Different genetic pathways in leukemogenesis for patients presenting with therapy-related myelodysplasia and therapy-related acute myeloid leukemia. Blood 86(9):3542−3552.

Pedersen-Bjergaard, J; Andersen, MK; Christiansen, DH. (2000) Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. Blood 95(11):3273−3279.

Pedersen-Bjergaard, J; Christiansen, DH; Desta, F; et al. (2006) Alternative genetic pathways and cooperating genetic abnormalities in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia 20(11):1943−1949.

Pedersen-Bjergaard, J; Andersen, MT; Andersen, MK. (2007) Genetic pathways in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. Hematology 21(3):392−397.

Pedersen-Bjergaard, J; Andersen, MK; Andersen, MT; et al. (2008) Genetics of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia 22(2):240−248.

Peterson LF; Boyapati A; Ahn EY; et al. (2007) Acute myeloid leukemia with the 8q22;21q22 translocation: secondary mutational events and alternative t(8;21) transcripts. Blood. 110(3):799-805.

Philip, P; Pedersen-Bjergaard, J. (1988) Cytogenetic, clinical, and cytologic characteristics of radiotherapy-related leukemias. Cancer Genet Cytogenet 31(2):227−236.

Popp, W; Vahrenholz, C; Schurfeld, C; et al. (1992) Investigations of the frequency of DNA strand breakage and cross-linking and of sister chromatid exchange frequency in the lymphocytes of patients with multiple myeloma undergoing cytostatic therapy with melphalan and prednisone. Carcinogenesis 13(11):2191−2195.

Povirk, LF; Shuker, DE. (1994) DNA damage and mutagenesis induced by nitrogen mustards. Mutat Res 318(3):205−226.

Praga, C; Bergh, J; Bliss, J; et al. (2005) Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. J Clin Oncol 23(18):4179−4191.

Preston, DL; Kusumi, S; Tomonaga, M; et al. (1994) Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950−1987. Radiat Res 137 (2 Suppl):S68−S97.

Preston, DL; Pierce, DA; Shimizu, Y; et al. (2004) Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res 162(4):377−389.

Preston, RJ. (2008) Update on linear non-threshold dose-response model and implications for diagnostic radiology procedures. Health Phys 95(5):541−546.

Preston, RJ; Fennell, TR; Leber, AP; et al. (1995) Reconsideration of the genetic risk assessment for ethylene oxide exposures. Environ Mol Mutagen 26(3):189−202.

Pui, CH; Relling, MV. (2000) Topoisomerase II inhibitor-related acute myeloid leukaemia. Br J Haematol 109:13−23.

Pui, CH; Behm, FG; Raimondi, SC; et al. (1989) Secondary acute myeloid leukemia in children treated for acute lymphoid leukemia [see comments in N Engl J Med 1989 321(3):185−187]. N Engl J Med 321(3):136−142.

Pui, C; Ribeiro, R; Hancock, M; et al. (1991) Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. N Engl J Med 325(24):1682−1687.

Pyatt, DW; Hays, SM; Cushing, CA. (2005) Do children have increased susceptibility for developing secondary acute myelogenous leukemia? Chem Biol Interact 153−154:223−229.

Pyatt, DW; Aylward, LL; Hays, SM. (2007) Is age an independent risk factor for chemically induced acute myelogenous leukemia in children? J Toxicol Environ Health B Crit Rev 10(5):379−400.

Qian, Z; Joslin, JM; Tennant, TR; et al. (2009) Cytogenetic and genetic pathways in therapy-related acute myeloid leukemia. Chem Biol Interact 184(1−2):50−57.

Qu, Q; Shore, R; Li, G; et al. (2002) Hematological changes among Chinese workers with a broad range of benzene exposures. Am J Ind Med 42(4):275−285.

Raposa, T; Varkonyi, J. (1987) The relationship between sister chromatid exchange induction and leukemogenicity of different cytostatics. Cancer Detect Prev 10(1−2):141−151.

Recio, L. (1997) Oncogene and tumor suppressor gene alterations in nasal tumors. Mutat Res 380(1−2):27−31.

Rege-Cambrin, G; Giugliano, E; Michaux, L; et al. (2005) Trisomy 11 in myeloid malignancies is associated with internal tandem duplication of both MLL and FLT3 genes. Haematologica 90(2):262−264.

Rinsky, RA; Hornung, RW; Silver, SR; et al. (2002) Benzene exposure and hematopoietic mortality: A long-term epidemiologic risk assessment. Am J Ind Med 42(6):474−480.

Rodjer, S; Swolin, B; Weinfeld, A; et al. (1990) Cytogenetic abnormalities in acute leukemia complicating melphalan-treated multiple myeloma. Cancer Genet Cytogenet 48:67−73.

Ron, E. (1998) Ionizing radiation and cancer risk: evidence from epidemiology. Radiat Res 150(5 Suppl):S30−S41.

Ron, E. (2003) Cancer risks from medical radiation. Health Phys 85:47−59.

Rothman, N; Smith, MT; Hayes, RB; et al. (1997) Benzene poisoning, a risk factor for hematological malignancy, is associated with the NQO1 609C-->T mutation and rapid fractional excretion of chlorzoxazone. Cancer Res 57(14):2839−2842.

Roumier, C; Fenaux, P; Lafage, M; et al. (2003) New mechanisms of AML1 gene alteration in hematological malignancies. Leukemia 17:9−16.

Russell, NH. (1997) Biology of acute leukaemia. Lancet 349(9045):118−122.

Sanderson, BJ; Shield, AJ. (1996) Mutagenic damage to mammalian cells by therapeutic alkylating agents. Mutat Res 355(1−2):41−57.

Sandoval, C; Pui, CH; Bowman, LC; et al. (1993) Secondary acute myeloid leukemia in children previously treated with alkylating agents, intercalating topoisomerase II inhibitors, and irradiation. J Clin Oncol 11(6):1039−1045.

Sankaranarayanan, K; Wassom, JS. (2008) Reflections on the impact of advances in the assessment of genetic risks of exposure to ionizing radiation on international radiation protection recommendations between the mid-1950s and the present. Mutat Res 658(1−2):1−27.

Savitz, DA; Andrews, KW. (1996) Risk of myelogenous leukaemia and multiple myeloma in workers exposed to benzene. Occup Environ Med 53(5):357−358.

Savitz, DA; Andrews, KW. (1997) Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. Am J Ind Med 31(3):287−295.

Sawyers, CL; Denny, CT; Witte, WN. (1991) Leukemia and the disruption of normal hematopoiesis. Cell 64(2):337−350.

Schonfeld, SJ; Gilbert, ES; Dores, GM; et al. (2006) Acute myeloid leukemia following Hodgkin lymphoma: a population-based study of 35,511 patients. J Natl Cancer Inst 98(3):215−218.

Schulz, C; von Andrian, UH; Massberg, S. (2009) Hematopoietic stem and progenitor cells: their mobilization and homing to bone marrow and peripheral tissue. Immunol Res 44(1−3):160−168.

Secretan, B; Straif, K; Baan, R; et al. (2009) A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 10(11):1033−1034.

Seedhouse, C; Russell, N. (2007) Advances in the understanding of susceptibility to treatment-related acute myeloid leukaemia. Br J Haematol 137(6):513−529.

Segel, GB; Lichtman, MA. (2004) Familial (inherited) leukemia, lymphoma, and myeloma: an overview. Blood Cells Mol Dis 32:246−261.

Seiber, SM; Adamson, RH. (1975) Toxicity of antineoplastic agents in man: chromosomal aberrations, antifertility effects, congenital malformations, and carcinogenic potential. Adv Cancer Res 22:57−155.

Shen, M; Lan, Q; Zhang, L; et al. (2006) Polymorphisms in genes involved in DNA double strand repair pathway and susceptibility to benzene-induced hematotoxicity. Carcinogenesis 27(10):2083−2089.

Silver, SR; Rinsky, RA; Cooper, SP; et al. (2002) Effect of follow-up time on risk estimates: a longitudinal examination of the relative risks of leukemia and multiple myeloma in a rubber hydrochloride cohort. Am J Ind Med 42(6):481−489.

Sinnett, D; Labuda, D; Krajinovic, M. (2006) Challenges identifying genetic determinants of pediatric cancers--the childhood leukemia experience. Fam Cancer 5:35−47.

Sirma, S; Agaoglu, L; Yildiz, I; et al. (2004) NAD(P)H:quinone oxidoreductase 1 null genotype is not associated with pediatric de novo acute leukemia. Pediatr Blood Cancer 43(5):568−570.

Smerhovsky, Z; Landa, K; Rossner, P; et al. (2001) Risk of cancer in an occupationally exposed cohort with increased level of chromosomal aberrations. Environ Health Perspect 109:41−45.

Smith, MA; Rubinstein, L; Cazenave, L; et al. (1993) Report of the Cancer Therapy Evaluation Program monitoring plan for secondary acute myeloid leukemia following treatment with epipodophyllotoxins. J Nat Cancer Inst 85(7):554−558.

Smith, MA; Rubinstein, L; Ungerleider, RS. (1994) Therapy-related acute myeloid leukemia following treatment with epipodophyllotoxins: estimating the risks. Med Pediatr Oncol 23(2):86−98.

Smith, MA; Rubinstein, L; Anderson, JR; et al. (1999) Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. J Clin Oncol 17(2):569−577.

Smith, MT; Wang, Y; Kane, E; et al. (2001) Low NAD(P)H:quinone oxidoreductase 1 activity is associated with increased risk of acute leukemia in adults. Blood 97(5):1422−1426.

Smith, MT; Wang, Y; Skibola, CF; et al. (2002) Low NAD(P)H:quinone oxidoreductase activity is associated with increased risk of leukemia with MLL translocations in infants and children. Blood 100(13):4590−4593.

Smith, MT; McHale, CM; Wiemels, JL; et al. (2005) Molecular biomarkers for the study of childhood leukemia. Toxicol Appl Pharmacol 206(2):237−245.

So, CW; Karsunky, H; Passegue, E; et al. (2003) MLL-GAS7 transforms multipotent hematopoietic progenitors and induces mixed lineage leukemias in mice. Cancer Cell 3(2):161−171.

Speit, G; Schmid, O; Frohler-Keller, M; et al. (2007) Assessment of local genotoxic effects of formaldehyde in humans measured by the micronucleus test with exfoliated buccal mucosa cells. Mutat Res 627(2):129−135.

Stanulla, M; Wang, J; Chervinsky, DS; et al. (1997) DNA cleavage within the MLL breakpoint cluster region is a specific event which occurs as part of higher-order chromatin fragmentation during the initial stages of apoptosis. Mol Cell Biol 17:4070−4079.

Steliarova-Foucher, E; Stiller, C; Kaatsch, P; et al. (2004) Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. Lancet 364(9451):2097−2105.

Storer, JB; Fry, RJM; Ullrich, RL. (1982) Somatic effects of radiation. In: Foster, HL; Small, JD; Fox, JG; eds. The mouse in biomedical research. New York, NY: Academic Press; pp. 138−144.

Stresemann, C; Lyko, F. (2008) Modes of action of the DNA methyltransferase inhibitors azacytidine and decitabine. Int J Cancer 123:8−13.

Sullivan, AK. (1993) Classification, pathogenesis, and etiology of neoplastic diseases of the hematopoietic system. In: Lee, GR; Bithell, TC; Foerster, J; et al.; eds. Wintrobe's clinical hematology, 9th Ed. Philadelphia, PA: Lea & Febiger; pp. 1725−1791.

Sun, P; Zhang, Z; Wan, J; et al. (2009) Association of genetic polymorphisms in GADD45A, MDM2, and p14 ARF with the risk of chronic benzene poisoning in a Chinese occupational population. Toxicol Appl Pharmacol 240:66−72.

Thomsen, JB; Schroder, H; Kristinsson, J; et al. (1999) Possible carcinogenic effect of 6-mercaptopurine on bone marrow stem cells: relation to thiopurine metabolism. Cancer 86(6):1080−1086.

Travis, LB; Fossa, SD; Schonfeld, SJ; et al. (2005) Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 97(18):1354−1365.

Tucker, MA; Meadows, AT; Boice, JD, Jr; et al. (1987) Leukemia after therapy with alkylating agents for childhood cancer. J Natl Cancer Inst 78(3):459−464.

Tucker, MA; Coleman, CN; Cox, RS; et al. (1988) Risk of second cancers after treatment for Hodgkin's disease. N Engl J Med 318(2):76−81.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). (2000a) Sources and effects of ionizing radiation, Vol. 1: Sources. UNSCEAR 2000 report to the General Assembly, with Scientific Annexes. New York, NY: The United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). (2000b) Sources and effects of ionizing radiation, Vol. 2: Effects. UNSCEAR 2000 report to the General Assembly, with Scientific Annexes. New York, NY: The United Nations.

U.S. EPA (Environmental Protection Agency). (1998) Carcinogenic effects of benzene: an update. National Center for Environmentla Assessment, Office of Research and Development, Washington, DC;EPA/600/P-97/001F. Available onine at http://www.epa.gov/ncea/pdfs/benzenef.pdf .

Utterback, DF; Rinsky, RA. (1995) Benzene exposure assessment in rubber hydrochloride workers: a critical evaluation of previous estimates. Am J Ind Med 27(5):661−676.

van Leeuwen, FE; Klokman, WJ; Hagenbeek, A; et al. (1994) Second cancer risk following Hodgkin's disease: a 20-year follow-up study. J Clin Oncol 12(2):312−325.

Vardiman, JW; Thiele, J; Arber, DA; et al. (2009) The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 114(5):937−951.

Vaughan, AT; Betti, CJ; Villalobos, MJ; et al. (2005) Surviving apoptosis: a possible mechanism of benzene-induced leukemia. Chem Biol Interact 153−154:179−185.

Vega-Stromberg, T. (2003) Chemotherapy-induced secondary malignancies. J Infus Nurs 26(6):353−361.

Vogel, EW; Barbin, A; Nivard, MJ; et al. (1998) Heritable and cancer risks of exposures to anticancer drugs: inter-species comparisons of covalent deoxyribonucleic acid-binding agents. Mutat Res 400(1−2):509−540.

Walker VE; Fennell TR; Upton PB; (1992) Molecular dosimetry of ethylene oxide: formation and persistence of 7-(2-hydroxyethyl)guanine in DNA following repeated exposures of rats and mice. Cancer Res. 52(16):4328-34.

Warner, JK; Wang, JC; Hope, KJ; et al. (2004) Concepts of human leukemic development. Oncogene 23(43):7164−7177.

Weiss, W. (1997) Cigarette smoking and lung cancer trends. A light at the end of the tunnel? Chest 111(5):1414−1416.

WHO (World Health Organization). (2001) Pathology and genetics: tumours of haematopoietic and lymphoid tissues. Jaffie, ES; Harris, NL; Stein, H; et al; eds.World Health Organization classification of tumours. Lyon, France: IARC Press.

WHO (World Health Organization). (2008) WHO classification of tumours of haematopoietic and lymphoid tissues. Fourth edition. Swerdlow, SH; Campo, E; Harris, NL; et al; eds.World Health Organization classification of tumours. Lyon, France: IARC Press.

Wiemels, JL; Pagnamenta, A; Taylor, GM; et al. (1999) A lack of a functional NAD(P)H:quinone oxidoreductase allele is selectively associated with pediatric leukemias that have MLL fusions. United Kingdom Childhood Cancer Study Investigators. Cancer Res 59(16):4095−4099.

Wiemels, JL; Zhang, Y; Chang, J; et al. (2005) RAS mutation is associated with hyperdiploidy and parental characteristics in pediatric acute lymphoblastic leukemia. Leukemia 19(3):415−419.

Williams, PR; Paustenbach, DJ. (2003) Reconstruction of benzene exposure for the Pliofilm cohort (1936-1976) using Monte Carlo techniques. J Toxicol Environ Health A 66(8):677−781.

Wison, A; Trumpp, A. (2008) Hematopoietic stem cell niches. In: Wickrema, A; Kee, B; eds. Molecular basis of hematopoiesis. New York, NY: Springer Science+Business Media; pp. 47−71.

Wong, O; Harris, F; Armstrong, TW; et al. (2010) A hospital-based case-control study of acute myeloid leukemia in Shanghai: Analysis of environmental and occupational risk factors by subtypes of the WHO classification. Chem Biol Interact. 184(1−2):112−128.

Worrillow, LJ; Travis, LB; Smith, AG; et al. (2003) An intron splice acceptor polymorphism in hMSH2 and risk of leukemia after treatment with chemotherapeutic alkylating agents. Clin Cancer Res 9(8):3012−3020.

Wright, EG. (1995) The pathogenesis of leukaemia. In: Hendry, JH; Lord, BI; eds. Radiation Toxicology: Bone Marrow and Leukemia. London: Taylor & Francis; pp. 245−274.

Wu, F; Zhang, Z; Wan, J; et al. (2008) Genetic polymorphisms in hMTH1, hOGG1 and hMYH and risk of chronic benzene poisoning in a Chinese occupational population. Toxicol Appl Pharmacol 233(3):447−453.

Xie, Y; Davies, SM; Xiang, Y; et al. (2003) Trends in leukemia incidence and survival in the United States (1973-1998). Cancer 97(9):2229−2235.

Xue, Y; Lu, D; Guo, Y; et al. (1992) Specific chromosomal translocations and therapy-related leukemia induced by bimolane therapy for psoriasis. Leuk Res 16(11):1113−1123.

Yenson, PR; Forrest, D; Schmiegelow, K; et al. (2008) Azathioprine-associated acute myeloid leukemia in a patient with Crohn's disease and thiopurine S-methyltransferase deficiency. Am J Hematol 83:80−83.

Yin, S; Li, G. (1994) Benzene risk and it prevention in China. In: Mehlman, MA; Upton, A; eds. The identification and control of environmental and occupational diseases: hazards and risks of chemicals in the oil refining industry. Princeton, NJ: Princeton Scientific Publishing Co; pp. 287−300.

Yin, S; Ye, P; Li, G; et al. (1994) Study on the program for diagnosis of benzene leukemia. In: Yin, S; Li, G; eds. Toxicological and epidemiological studies on benzene in china. Institute of Occcupation Medicine, Chinese Academy of Preventive Medicine, Beijing.

Zarbl, H. (2006) Cellular oncogenes and carcinogenesis. In: Warshawsky, D; Landolph, JRJ; eds. Molecular carcinogenesis and the molecular biology of cancer. New York, NY: Taylor and Francis; pp. 103−129.

Zhang, L; Steinmaus, C; Eastmond, DA; et al. (2009) Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. Mutat Res 681(2−3):150−168.

Zhang, L; Tang, X; Rothman, N; et al. (2010) Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells. Cancer Epidemiol Biomarkers Prev 19:80−88.

Zhang, MH; Wang, XY; Gao, LS. (1993) [140 cases of acute leukemia caused by bimolane]. Chung Hua Nei Ko Tsa Chih 32(10):668−672.

Zhang, Y; Rowley, JD. (2006) Chromatin structural elements and chromosomal translocations in leukemia. DNA Repair (Amst). 5(9−10):1282−1297.

Zheng, S; Ma, X; Zhang, L; et al. (2004) Hypermethylation of the 5' CpG island of the FHIT gene is associated with hyperdiploid and translocation-negative subtypes of pediatric leukemia. Cancer Res 64(6):2000−2006.